

Page 3 [Amendment Under 37 C.F.R. §1.116 (In Response  
To The October 8, 2002 Office Action) – October 28, 2002]



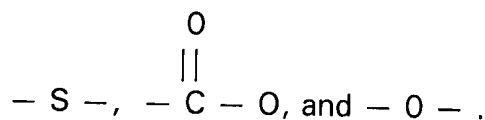
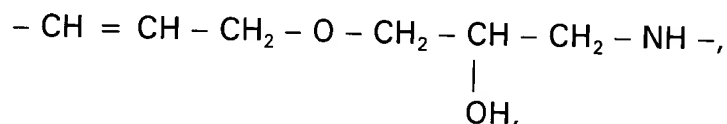
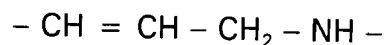
**KINDLY AMEND THE ABOVE-IDENTIFIED APPLICATION AS FOLLOWS:**

**In The Claims:**

Please enter new replacement claims 581, 583, 601, 603, 622, 624, 642, 644, 663, 665, 682, 684, 702, 704, 721, 723, 736, 740, 741, 748, 751, 755, 759, 760, 767, 770, 775, 779, 780, 787, 790, 794, 798, 799, 806, 809, 814, 816, 817, 819, 820, 822, 823 and 825 as follows:

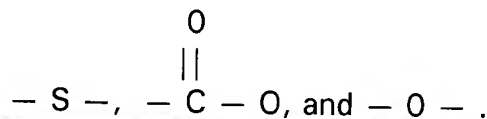
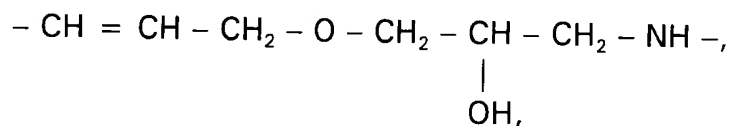
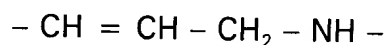
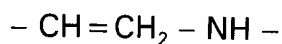
~~5~~  
581. (Amended) The oligo- or polydeoxyribonucleotide of claim ~~576~~<sup>1</sup>, wherein said chemical linkage comprises a -CH<sub>2</sub>NH- moiety.

583. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>1</sup>576, wherein said chemical linkage comprises any of the moieties:



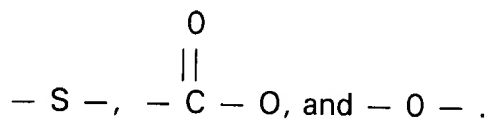
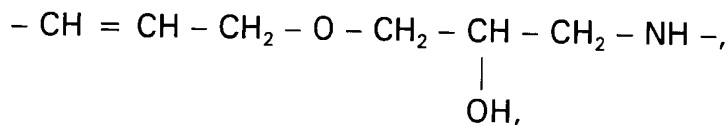
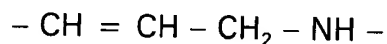
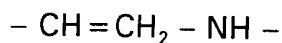
~~601~~. (Amended) The oligo- or polydeoxyribonucleotide of claim ~~596~~<sup>20</sup>, wherein said chemical linkage comprises a -CH<sub>2</sub>NH- moiety.

<sup>26</sup>  
~~603~~. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>29</sup>~~596~~, wherein said chemical linkage comprises any of the moieties:



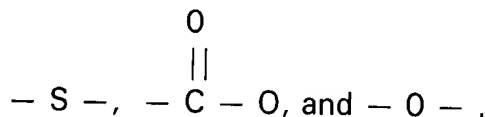
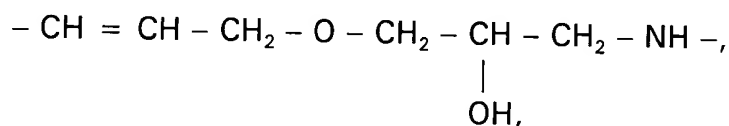
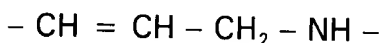
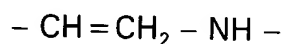
<sup>44</sup>  
~~622~~. (Amended) The oligo- or polynucleotide of claim <sup>40</sup>~~617~~, wherein said chemical linkage comprises a  $-CH_2NH-$  moiety.

<sup>46</sup>  
~~624~~. (Amended) The oligo- or polynucleotide of claim <sup>40</sup>~~617~~, wherein said chemical linkage comprises any of the moieties:



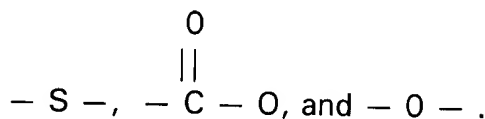
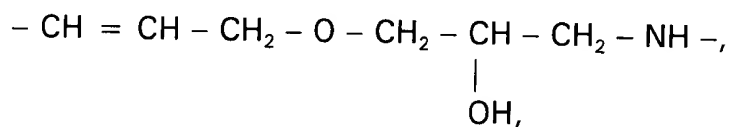
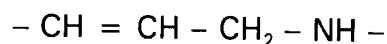
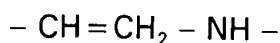
<sup>63</sup>  
~~642~~. (Amended) The oligo- or polynucleotide of claim <sup>59</sup>~~637~~, wherein said chemical linkage comprises a  $-CH_2NH-$  moiety.

<sup>16</sup>  
644. (Amended) The oligo- or polynucleotide of claim <sup>59</sup>~~637~~, wherein said chemical linkage comprises any of the moieties:



<sup>09</sup> <sup>83</sup>  
663. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>79</sup>~~658~~, wherein said chemical linkage comprises a  $-CH_2NH-$  moiety.

<sup>010</sup> <sup>85</sup>  
665. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>79</sup>~~658~~, wherein said chemical linkage comprises any of the moieties:



<sup>011</sup> <sup>101</sup>  
682. (Amended) The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage comprises a  $-CH_2NH-$  moiety.

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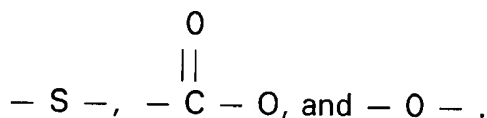
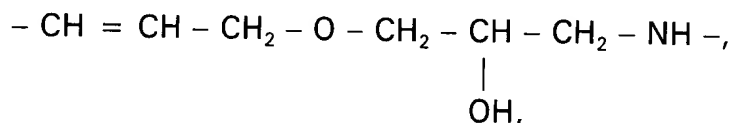
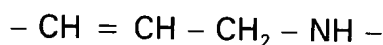
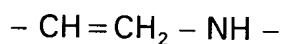
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103/

684. (Amended) The oligo- or polydeoxyribonucleotide of claim ~~677~~<sup>97</sup>, wherein said chemical linkage comprises any of the moieties:



012

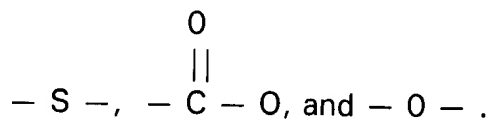
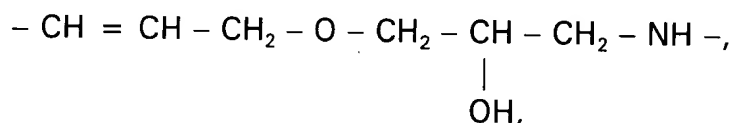
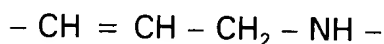
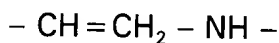
013

120/

702. (Amended) The oligo- or polynucleotide of claim ~~697~~<sup>116</sup>, wherein said chemical linkage comprises a  $-CH_2NH-$  moiety.

122/

704. (Amended) The oligo- or polynucleotide of claim ~~697~~<sup>116</sup>, wherein said chemical linkage comprises any of the moieties:



014

015

138/

721. (Amended) The oligo- or polynucleotide of claim ~~716~~<sup>134</sup>, wherein said chemical linkage comprises a  $-CH_2NH-$  moiety.



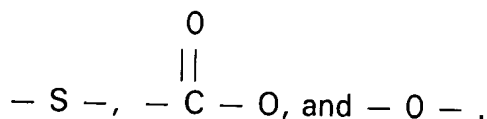
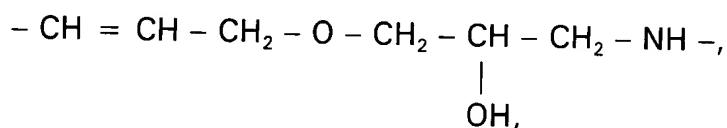
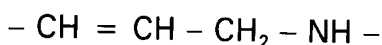
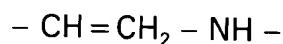
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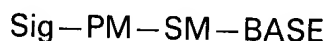
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<sup>140</sup>  
~~723~~. (Amended) The oligo- or polynucleotide of claim <sup>134</sup>~~716~~, wherein said chemical linkage comprises any of the moieties:



<sup>153</sup>  
~~736~~. (Amended) An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the formula



wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a base moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM through a chemical linkage comprising a polypeptide, and said Sig comprising a non-radioactive label moiety which can be directly detected when indirectly attached to PM through said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

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156

018 740. (Amended) The oligo- or polydeoxyribonucleotide of claim 153 736, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

157

741. (Amended) The oligo- or polydeoxyribonucleotide of claim 153 736, wherein said PM is monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached via said polypeptide chemical linkage to said PM through a phosphorus atom or phosphate oxygen.

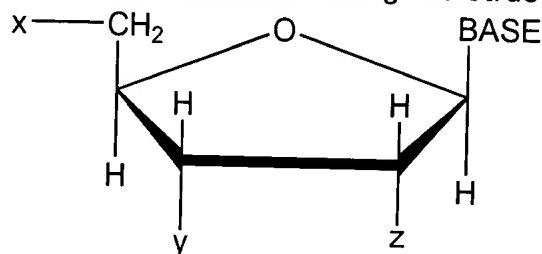
164

019 748. (Amended) The oligo- or polydeoxyribonucleotide of claim 153 736, wherein said oligo- or polydeoxyribonucleotide is terminally ligated or attached to said polypeptide chemical linkage.

167

020 751. (Amended) The oligo- or polydeoxyribonucleotide of claim 153 736, wherein said Sig moiety is attached via said polypeptide chemical linkage to a phosphate moiety in a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

171  
755. (Amended) An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the structural formula:



021  
wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

wherein Sig is covalently attached through a chemical linkage to at least one phosphate selected from the group consisting of x, y, z, and a combination thereof, said chemical linkage comprising a polypeptide, and said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to said phosphate via said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polydeoxynucleotide or when said oligo- or polydeoxynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

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022 <sup>174</sup>  
~~759~~. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>171</sup>~~755~~, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

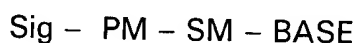
<sup>175</sup>  
~~760~~. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>171</sup>~~755~~, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and said Sig moiety is covalently attached via said polypeptide chemical linkage to either or both of said x and y through a phosphorus atom or phosphate oxygen.

023 <sup>182</sup>  
~~767~~. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>171</sup>~~755~~, wherein said oligo- or polydeoxyribonucleotide is terminally ligated or attached to said polypeptide chemical linkage.

024 <sup>185</sup>  
~~770~~. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>171</sup>~~755~~, wherein said Sig moiety is attached via said polypeptide chemical linkage to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

190

~~775~~. (Amended) An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the formula



025 wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM via a chemical linkage comprising a polypeptide, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to PM via said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide, and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

193

026 ~~779~~. (Amended) The oligo- or polynucleotide of claim ~~775~~<sup>190</sup>, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

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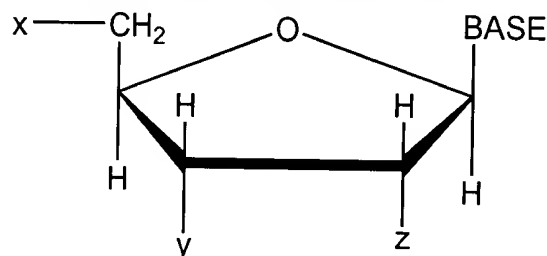
026  
cont. <sup>194</sup>  
~~780~~. (Amended) The oligo- or polynucleotide of claim <sup>190</sup>~~775~~, wherein said PM  
is a monophosphate, a diphosphate or a triphosphate and said Sig moiety is  
covalently attached via said polypeptide chemical linkage to said PM through  
a phosphorus atom or a phosphate oxygen.

027 <sup>201</sup>  
~~787~~. (Amended) The oligo- or polynucleotide of claim <sup>190</sup>~~775~~, wherein said oligo- or  
polynucleotide is terminally ligated or attached to said polypeptide chemical linkage.

028 <sup>204</sup>  
~~790~~. (Amended) The oligo- or polynucleotide of claim <sup>190</sup>~~775~~, wherein said Sig  
moiety is attached via said polypeptide chemical linkage to a terminal nucleotide in  
said oligo- or polynucleotide.

208  
794

(Amended) An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the structural formula:



029 wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

wherein Sig is covalently attached through a chemical linkage to at least one phosphate selected from the group consisting of x, y and z, and a combination thereof, said chemical linkage comprising a polypeptide, and said Sig comprising a non-radioactive label moiety which can be directly detected when attached to said phosphate via said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a

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029  
cont polyribonucleotide and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

211  
798. (Amended) The oligo- or polynucleotide of claim <sup>208</sup>794, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

030  
212  
799. (Amended) The oligo- or polynucleotide of claim <sup>208</sup>794, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and Sig moiety is covalently attached via said polypeptide chemical linkage to either or both of said x and y through a phosphorus atom or a phosphate oxygen.

031  
219  
806. (Amended) The oligo- or polynucleotide of claim <sup>208</sup>794, wherein said oligo- or polynucleotide is terminally ligated or attached to said polypeptide chemical linkage.

032  
222  
809. (Amended) The oligo- or polynucleotide of claim <sup>208</sup>794, wherein said Sig moiety is attached via said polypeptide chemical linkage to a terminal nucleotide in said oligo- or polynucleotide.

033  
227  
814. (Amended) The oligo- or polydeoxyribonucleotide of claims <sup>1</sup>576 or <sup>79</sup>658, wherein said Sig is covalently attached to PM through a chemical linkage comprising a polypeptide.



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034 <sup>229</sup>  
816. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>227</sup>~~814~~, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

<sup>230</sup>  
817. (Amended) The oligo- or polydeoxyribonucleotide of claims <sup>20</sup>~~596~~ or <sup>97</sup>~~677~~, wherein said Sig is covalently attached to said at least one phosphate through a chemical linkage comprising a polypeptide.

035 <sup>232</sup>  
819. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>23</sup>~~817~~, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

<sup>233</sup>  
820. (Amended) The oligo- or polynucleotide of claims <sup>40</sup>~~617~~ or <sup>116</sup>~~697~~, wherein said Sig is covalently attached to PM via a chemical linkage comprising a polypeptide.

036 <sup>235</sup>  
822. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>233</sup>~~820~~, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

<sup>236</sup>  
823. (Amended) The oligo- or polynucleotide of claims <sup>59</sup>~~637~~ or <sup>134</sup>~~716~~, wherein said Sig is covalently attached to said at least one phosphate through a chemical linkage comprising a polypeptide.

037 <sup>238</sup>  
825. (Amended) The oligo- or polydeoxyribonucleotide of claim <sup>237</sup>~~824~~, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

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✓  
Cancel claims 577, 597, 618, 638, 659, 678, 698, 717, 737, 756, 776 and  
795.

\* \* \* \* \*

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### REMARKS

Claims 576-825 were previously pending in this application. Claims 581, 583, 601, 603, 622, 624, 642, 644, 663, 665, 682, 684, 702, 704, 721, 723, 736, 740-741, 748, 751, 755, 759-760, 767, 770, 775, 779-780, 787, 790, 794, 798-799, 806, 809, 814, 816-817, 819, 820, 822-823 and 825 have been amended. Claims 577, 597, 618, 638, 659, 678, 698, 717, 737, 756, 776 and 795 have been canceled. Accordingly, claims 576, 578-596, 598-617, 619-637, 639-658, 660-677, 679-697, 699-716, 718-736, 738-755, 757-775, 777-794 and 796-825 are presented for further examination on the merits.

#### I. Claim Amendments

In a sincere effort to place their application in allowable condition, Applicants have amended a number of rejected claims. These amendments are described below.

First, an informality in the form of an improper dependency has been corrected in claim 814. See page 2, item no. 3 in the October 8, 2002 Office Action. This claim previously depended from a canceled claim (454). As amended above, claim 814 now depends from claims 576 or 658. This correction also affects claims 815 and 816 which depend directly from claim 814.

Second, in claims 581, 583, 601, 603, 622, 624, 642, 644, 663, 665, 682, 684, 702, 704, 721 and 723, Applicants have deleted language relating to the chemical linkage being an olefinic bond at the  $\alpha$ -position relative to a point of attachment to the nucleotide. See pages 4-5, item no. 7 in the October 8, 2002 Office Action. Thus, for example, amended claim 581 now recites "[t]he oligo- or

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polydeoxyribonucleotide of claim 576, wherein said chemical linkage comprises a  
comprises a  $\text{-CH}_2\text{NH-}$  moiety."

Third, as indicated above, claims 577, 597, 618, 638, 659, 678, 698, 717, 737, 756, 776 and 795 have been canceled. These canceled claims were drawn to subject matter the non-radioactive label moiety Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide "self-signaling or self-indicating or self-detecting." See pages 2-4, item no. 5 in the October 8, 2002 Office Action.

Fourth, reference to the chemical linkage being "a protein" has been removed altogether from claims 736, 740-741, 748, 751, 755, 759-760, 767, 770, 775, 779-780, 787, 790, 794, 798-799, 806, 809, 814, 816-817, 819-820, 822-823 and 825. As amended, each of these claims is now drawn to a chemical linkage comprising a *polypeptide*. The impetus for removing "protein" from Applicants' claimed chemical linkage comes from item no. 8, page 5 in the October 8, 2002 Office Action.

Finally, in conjunction with these last-described amendments, a minor misspelling in claim 741 ("oxyxgen") has been corrected. The word "through" has been inserted in claims 760 and 799, these claims now reciting " . . . and said Sig moiety is covalently attached via said polypeptide chemical linkage to either or both of said x and y *through* a phosphorus atom or phosphate oxygen." Further, the phrase "or derived" has been inserted in claims 816, 819 and 822. These claims now recite "wherein said polypeptide is selected *or derived* from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin."

It is believed that the above amendments to the claims are necessary to meet the objections or to adopt the Examiner's suggestions as set forth in the Office Action. Because these amendments serve to limit -- rather than to expand - the scope of Applicants' claimed invention, no new issues are raised that would

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require further consideration and/or search by the Examiner. Furthermore, because they are limiting and not expansive, these claim amendments do not raise any issues of new matter. Moreover, these amendments to the claims, including several claim cancellations, are believed to place this application in better form for appeal by materially reducing or simplifying the issues for appeal. Finally, no additional claims are presented; instead, twelve claims have been canceled without any additional claims being added.

As required under Simplified Amendment Practice. Replacement paragraphs/sections/claims to be used. 37 CFR 1.121, and as set forth in the Changes to the Patent Rules (37 CFR 1.121 MPEP Bookmark, Volume 1, Issue 3), a marked-up version of the claims amended above is attached as Exhibit A. This marked-up version is entitled "Marked-Up Version Of Amended Claims."

Although not required, Applicants have also attached a consolidation set of claims that reflect the pending claims in this application following entry of the above claim amendments and cancellations. The consolidated set of pending claims is attached as Exhibit B.

Entry of the above amendments and claim cancellations is respectfully requested.

## **II. Claim Objections (Informalities)**

Claims 814-816 stand objected to because of informalities due to their depending from canceled claim 454. See Office Action, item 3, page 2.

It is believed that the amendments to claim 814 above corrects the informality.

**III. The Rejection Under 35 U.S.C. §112, Second Paragraph**

Claims 577, 597, 618, 638, 659, 678, 698, 717, 737, 756, 776, 795 stand rejected for indefiniteness under 35 U.S.C. §112, second paragraph. In the October 8, 2002 Office Action (pages 3-4), the Examiner stated that these claims

are indefinite over the recitation of "self-signaling or self-indicating or self-detecting" because it is not clear what is meant by this recitation. (i.e. it is not clear as to how a Sig can be considered be self-signaling or self-indicating or self-detecting). For example, a fluorescent compound needs a specific wavelength of light to excite the compound to fluoresce and optical detection system to detect emitted fluorescence, therefore it is not clear as to how a Sig (for example a fluorescent compound) could be self-signaling or self-indicating or self-detecting. In other words, it is not clear as to how a Sig can be considered self-signaling or self-indicating or self-detecting without the use of an additional element to aid in the signaling, indicating or detecting of the Sig.

**Applicants Arguments**

Applicants' argue that a reader skilled in the art would readily comprehend the meaning of the above terms. Furthermore, Applicants identity 4 US patents and 4 scientific publications to demonstrate that the term "self-indicating" is used and recognized in the art.

**Response to Applicants Arguments**

Applicants arguments have been considered but are not persuasive for the following reasons:

1) Given the lack of a definition in the specification for "self-signaling", "self-indicating" or "self-detecting", it is not clear that a reader skilled in the art would readily comprehend the meaning of these terms. Claim 577, states, "wherein Sig is or renders ...self-detecting", does this mean that a fluorescent label could detect itself?

2) The cited US patents and literature articles, while using the term "self-indicating", have nothing to do with the claimed invention. The claimed invention is drawn to a Sig that is part of a modified nucleotide of a polydeoxyribonucleotide, the cited references do not involve modified nucleotides. Furthermore, these references do not use the terms, "self-signaling" or "self-detecting", and therefore, do help render these terms definite.

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The rejection for indefiniteness is respectfully traversed.

As indicated in the opening remarks of this paper, claims 577, 597, 618, 638, 659, 678, 698, 717, 737, 756, 776 and 795 have been canceled. The cancellation of these claims is believed to have rendered the indefiniteness grounds moot.

Reconsideration and withdrawal of the rejection under §112, second paragraph, are respectfully requested.

**III. The First Rejection Under 35 U.S.C. §112, First Paragraph (New Matter)**

Claims 581, 583, 601, 603, 622, 624, 642, 644, 663, 665, 682, 684, 702, 704, 721, and 723 stand rejected for new matter under 35 U. S. C. §112, first paragraph. In the Office Action (pages 4-5), the Examiner stated:

These claims include the recitation of "wherein chemical linkage comprises or includes an olefinic bond at the alpha-position relative to the point of attachment". The only reference to a "chemical linkage" is the Sig is covalently attached to the PM directly or through a chemical linkage. There is no support in the specification, for where the Sig is covalently attached to the PM directly or through a chemical linkage, "wherein chemical linkage comprises or includes an olefinic bond at the alpha-position relative to the point of attachment". This recitation is considered new matter.

Applicants argue that the new recitation is properly supported by Applicant's original disclosure, page 3, lines 2-3 from bottom of the page; page 11, line 7 in the second paragraph; and originally filed claim 78. However, these references to the specification do not describe the Sig is covalently attached to the PM directly or through a chemical linkage, "wherein chemical linkage comprises or includes an olefinic bond at the alpha-position relative to the point of attachment".

These references actually teach that the position in question (i.e. alpha-position relative to the point of attachment) is relative to the point of attachment to the Base, not the Sig-PM attachment, as instantly claimed.

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The first new matter rejection is respectfully traversed.

As indicated in the opening remarks of this paper, claims 736, 740-741, 748, 751, 755, 759-760, 767, 770, 775, 779-780, 787, 790, 794, 798-799, 806, 809, 814, 816-817, 819-820, 822-823 and 825 have each been amended to delete the language at issue in the first rejection for new matter. Thus, the recitation that the chemical linkage comprises *an olefinic bond at the  $\alpha$ -position relative to a point of attachment* to the nucleotide has been expunged from the rejected claims.

In light of the above amendments to these claims, Applicants respectfully request reconsideration and withdrawal of the first new matter rejection.

**IV. The Second Rejection Under 35 U.S.C. §112, First Paragraph (New Matter)**

Claims 736-825 stand rejected for new matter under 35 U.S.C. §112, first paragraph. In the Office Action (page 5), the Examiner stated:

These claims recite, "Sig being covalently attached to PM through a chemical linkage comprising a polypeptide or a protein", which is not supported in the specification, and therefore, constitutes new matter.

If Applicants' traverse this rejection, Applicants' should specifically identify (by page and line number), where the specification provides support for these claims. Conclusion 9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action.

The second new matter rejection is respectfully traversed.

As indicated in the opening remarks to this paper, Applicants have removed language from the rejected claims in which the chemical linkage comprises a



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*protein*. As amended, claims 736-825 are drawn to subject matter in which the chemical linkage comprises a *polypeptide*.

In response the issue relating to chemical linkage comprising a polypeptide, Applicants are submitting herewith the Supplemental Declaration of Dr. Charles W. Parker, who is the same declarant referenced on page 2 in the October 8, 2002 Office Action. A copy of Dr. Parker's Supplemental Declaration is attached as Exhibit C.

In his Supplemental Declaration (Exhibit C), Dr. Parker explains his reasons as a person skilled in the art why Applicants' claimed subject matter in which the chemical linkage comprises a polypeptide is supported by their originally filed disclosure. In particular, Dr. Parker points to Applicants' originally filed claims 141, 143 and 167 and Example V, page 57 in the Engelhardt specification. Dr. Parker's comments in this regard are found in sections 6-8, pages 5-7 in his Supplemental Declaration. Furthermore, in Section 9 (pages 7-8) of his Supplemental Declaration (Exhibit C), Dr. Parker summarizes his opinion and conclusion that "the Engelhardt specification . . . reasonably conveys that Applicants had possession of their claimed subject matter wherein non-radioactive label moieties Sig are covalently attached to phosphate moieties through chemical linkages comprising polypeptides."

In view of the above claim amendments and Dr. Parker's Supplemental Declaration (Exhibit C), including his statements that point out with particularity the support of claims 736-825 wherein the chemical linkage comprises a polypeptide, Applicants respectfully request reconsideration and withdrawal of the second new matter rejection.

Favorable action is respectfully solicited.

\* \* \* \* \*

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### SUMMARY AND CONCLUSIONS

Claims 576, 578-596, 598-617, 619-637, 639-658, 660-677, 679-697, 699-716, 718-736, 738-755, 757-775, 777-794 and 796-825 continue to be presented for examination in this application. Claims 581, 583, 601, 603, 622, 624, 642, 644, 663, 665, 682, 684, 702, 704, 721, 723, 736, 740-741, 748, 751, 755, 759-760, 767, 770, 775, 779-780, 787, 790, 794, 798-799, 806, 809, 814, 816-817, 819, 820, 822-823 and 825 have been amended. Claims 577, 597, 618, 638, 659, 678, 698, 717, 737, 756, 776 and 795 have been canceled. No claims have been added by this paper.

No fee or fees are believed due for this paper, this response being filed within the first month after the mailing of the October 8, 2002 Office Action. In the event that any other fee or fees are due, however, authorization is hereby given to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully Submitted,



Ronald C. Fedus  
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Exhibit A To Applicants' October 28, 2002 Amendment Under §1.116  
(In Response To The October 8, 2002 Office Action)

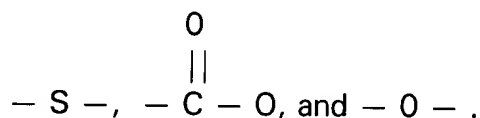
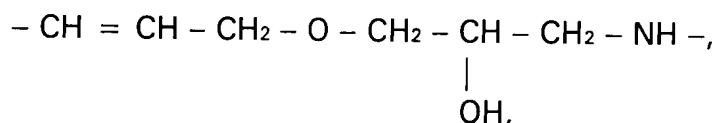
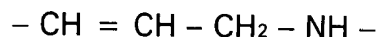
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MARKED-UP VERSION OF AMENDED CLAIMS

581. (Amended) The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage comprises a [~~member selected from the group consisting of an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, a~~]-CH<sub>2</sub>NH- moiety[~~, or both~~].

583. (Amended) The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage comprises [~~or includes an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, or~~] any of the moieties:



601. (Amended) The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage comprises a [~~member selected from the group consisting of an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, a~~]-CH<sub>2</sub>NH- moiety[~~, or both~~].

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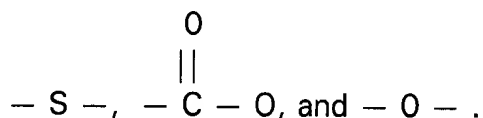
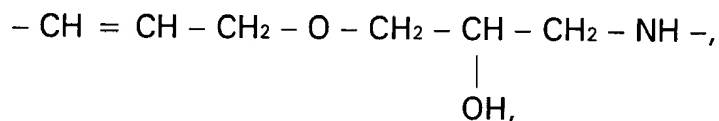
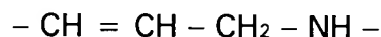
Filed: June 7, 1995

Page 2 [Marked-Up Version of Amended Claims (Exhibit A) to Applicants'

October 28, 2002 Amendment Under 37 C.F.R. §1.116

(In Response To The October 8, 2002 Office Action)]

603. (Amended) The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage comprises ~~[or includes an olefinic bond at the  $\alpha$  position relative to the point of attachment to x, y or z, or]~~ any of the moieties:



622. (Amended) The oligo- or polynucleotide of claim 617, wherein said chemical linkage comprises a ~~[member selected from the group consisting of an olefinic bond at the  $\alpha$  position relative to the point of attachment to the nucleotide, a]~~  $-CH_2NH-$  moiety~~[, or both]~~.

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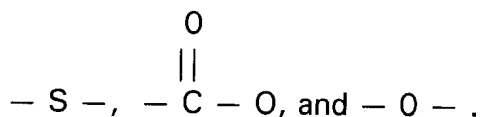
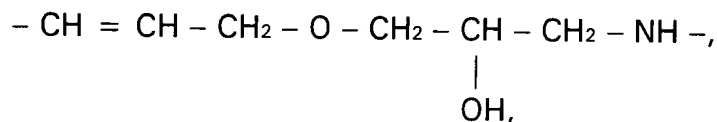
Filed: June 7, 1995

Page 3 [Marked-Up Version of Amended Claims (Exhibit A) to Applicants'

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624. (Amended) The oligo- or polynucleotide of claim 617, wherein said chemical linkage comprises ~~[or includes an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, or]~~ any of the moieties:



642. (Amended) The oligo- or polynucleotide of claim 637, wherein said chemical linkage comprises a ~~[member selected from the group consisting of an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, a]~~  $-CH_2NH-$  moiety~~[, or both]~~.

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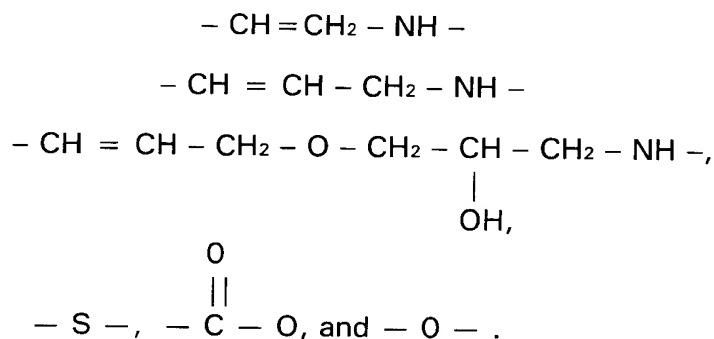
Filed: June 7, 1995

Page 4 [Marked-Up Version of Amended Claims (Exhibit A) to Applicants'

October 28, 2002 Amendment Under 37 C.F.R. §1.116

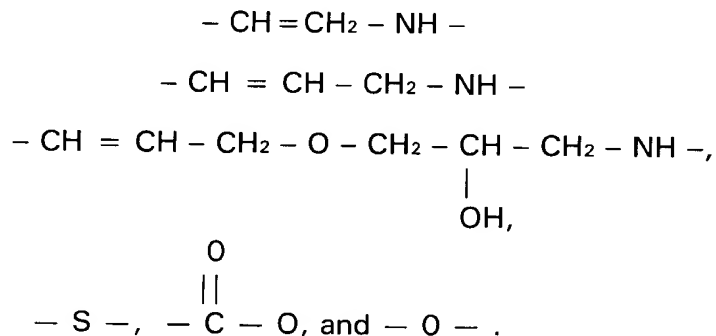
(In Response To The October 8, 2002 Office Action)]

644. (Amended) The oligo- or polynucleotide of claim 637, wherein said chemical linkage comprises ~~[or includes an olefinic bond at the  $\alpha$ -position relative to x, y or z,~~  
or] any of the moieties:



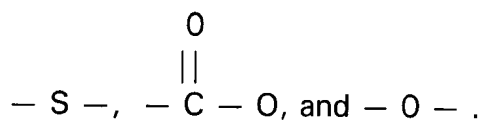
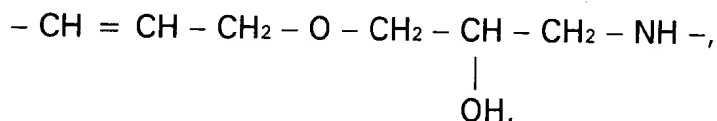
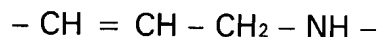
663. (Amended) The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage comprises a ~~[member selected from the group consisting of an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, a]~~  
-CH<sub>2</sub>NH- moiety~~[, or both]~~.

665. (Amended) The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage comprises ~~[or includes an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, or]~~ any of the moieties:



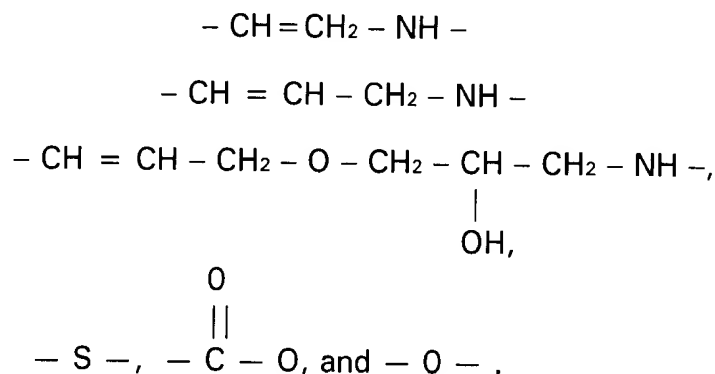
682. (Amended) The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage comprises a ~~[member selected from the group consisting of an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, a]~~ -CH<sub>2</sub>NH- moiety~~[, or both]~~.

684. (Amended) The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage comprises ~~[or includes an olefinic bond at the  $\alpha$ -position relative to the point of attachment to x, y or z, or]~~ any of the moieties:



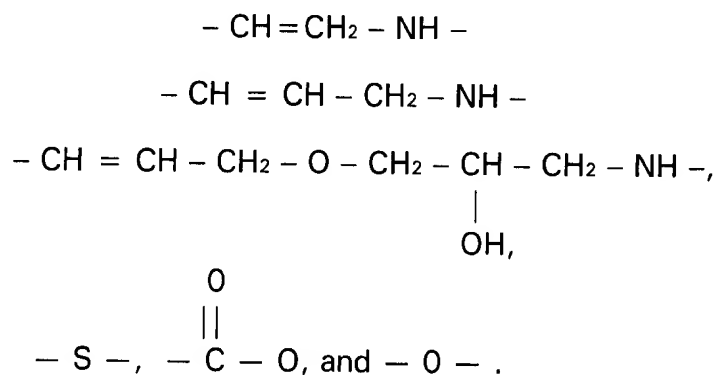
702. (Amended) The oligo- or polynucleotide of claim 697, wherein said chemical linkage comprises a ~~[member selected from the group consisting of an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, a]~~ -CH<sub>2</sub>NH- moiety~~[, or both]~~.

704. (Amended) The oligo- or polynucleotide of claim 697, wherein said chemical linkage comprises ~~[or includes an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, or]~~ any of the moieties:



721. (Amended) The oligo- or polynucleotide of claim 716, wherein said chemical linkage comprises a ~~[member selected from the group consisting of an olefinic bond at the  $\alpha$ -position relative to the point of attachment to the nucleotide, a]~~  $-\text{CH}_2\text{NH}-$  moiety~~[, or both]~~.

723. (Amended) The oligo- or polynucleotide of claim 716, wherein said chemical linkage comprises ~~[or includes an olefinic bond at the  $\alpha$ -position relative to x, y or z, or]~~ any of the moieties:





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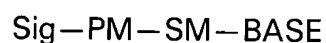
Filed: June 7, 1995

Page 7 [Marked-Up Version of Amended Claims (Exhibit A) to Applicants'

October 28, 2002 Amendment Under 37 C.F.R. §1.116

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736. (Amended) An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the formula



wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a base moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM through a chemical linkage comprising a polypeptide [~~or a protein~~], and said Sig comprising a non-radioactive label moiety which can be directly detected when indirectly attached to PM through said polypeptide [~~or protein~~] chemical linkage or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

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Page 8 [Marked-Up Version of Amended Claims (Exhibit A) to Applicants'

October 28, 2002 Amendment Under 37 C.F.R. §1.116

(In Response To The October 8, 2002 Office Action)]

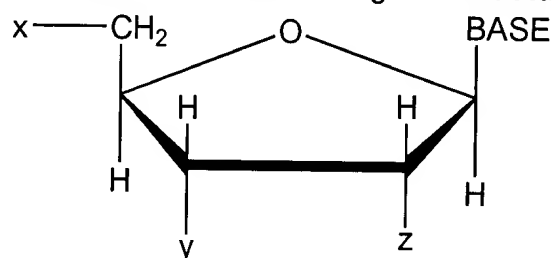
740. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said polypeptide [~~or protein~~] chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

741. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said PM is monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached via said polypeptide [~~or protein~~] chemical linkage to said PM through a phosphorus atom or phosphate [~~oxygen~~] oxygen.

748. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said oligo- or polydeoxyribonucleotide is terminally ligated or attached to said polypeptide [~~or protein~~] chemical linkage.

751. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said Sig moiety is attached via said polypeptide [~~or protein~~] chemical linkage to a phosphate moiety in a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

755. (Amended) An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein  $x$  is selected from the group consisting of  $\text{H}-$ ,  $\text{HO}-$ , a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein  $y$  is selected from the group consisting of  $\text{H}-$ ,  $\text{HO}-$ , a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein  $z$  is selected from the group consisting of  $\text{H}-$ ,  $\text{HO}-$ , a mono-phosphate, a di-phosphate and a tri-phosphate; and

wherein Sig is covalently attached through a chemical linkage to at least one phosphate selected from the group consisting of  $x$ ,  $y$ ,  $z$ , and a combination thereof, said chemical linkage comprising a polypeptide [~~or a protein~~], and said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to said phosphate via said polypeptide [~~or protein~~] chemical linkage or when said modified nucleotide is incorporated into said oligo- or polydeoxynucleotide or when said oligo- or polydeoxynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

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Page 10 [Marked-Up Version of Amended Claims (Exhibit A) to Applicants'

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(In Response To The October 8, 2002 Office Action)]

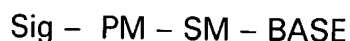
759. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said polypeptide [~~or-protein~~] chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

760. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and said Sig moiety is covalently attached via said polypeptide [~~or-protein~~] chemical linkage to either or both of said x and y through a phosphorus atom or phosphate oxygen.

767. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said oligo- or polydeoxyribonucleotide is terminally ligated or attached to said polypeptide [~~or-protein~~] chemical linkage.

770. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said Sig moiety is attached via said polypeptide [~~or-protein~~] chemical linkage to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

775. (Amended) An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the formula



wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM via a chemical linkage comprising a polypeptide [~~or a protein~~], said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to PM via said polypeptide [~~or protein~~] chemical linkage or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide, and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

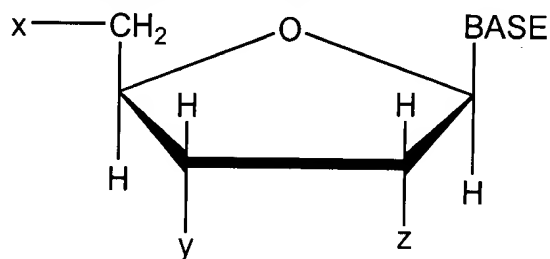
779. (Amended) The oligo- or polynucleotide of claim 775, wherein said polypeptide [~~or protein~~] chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

780. (Amended) The oligo- or polynucleotide of claim 775, wherein said PM is a monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached via said polypeptide [~~or-protein~~] chemical linkage to said PM through a phosphorus atom or a phosphate oxygen.

787. (Amended) The oligo- or polynucleotide of claim 775, wherein said oligo- or polynucleotide is terminally ligated or attached to said polypeptide [~~or-protein~~] chemical linkage.

790. (Amended) The oligo- or polynucleotide of claim 775, wherein said Sig moiety is attached via said polypeptide [~~or-protein~~] chemical linkage to a terminal nucleotide in said oligo- or polynucleotide.

794. (Amended) An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-

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Page 13 [Marked-Up Version of Amended Claims (Exhibit A) to Applicants'

October 28, 2002 Amendment Under 37 C.F.R. §1.116

(In Response To The October 8, 2002 Office Action)]

phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H— , HO— , a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H— , HO— , a mono-phosphate, a di-phosphate and a tri-phosphate; and

wherein Sig is covalently attached through a chemical linkage to at least one phosphate selected from the group consisting of x, y and z, and a combination thereof, said chemical linkage comprising a polypeptide [~~or a protein~~], and said Sig comprising a non-radioactive label moiety which can be directly detected when attached to said phosphate via said polypeptide [~~or protein~~] chemical linkage or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

798. (Amended) The oligo- or polynucleotide of claim 794, wherein said polypeptide [~~or protein~~] chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

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799. (Amended) The oligo- or polynucleotide of claim 794, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or a phosphate oxygen.

806. (Amended) The oligo- or polynucleotide of claim 794, wherein said oligo- or polynucleotide is terminally ligated or attached to said polypeptide [~~or protein~~] chemical linkage.

809. (Amended) The oligo- or polynucleotide of claim 794, wherein said Sig moiety is attached via said polypeptide [~~or protein~~] chemical linkage to a terminal nucleotide in said oligo- or polynucleotide.

814. (Amended) The oligo- or polydeoxyribonucleotide of claims [454] 576 or 658, wherein said Sig is covalently attached to PM through a chemical linkage comprising a polypeptide [~~or a protein~~].

816. The oligo- or polydeoxyribonucleotide of claim 814, wherein said polypeptide [~~or protein~~] is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

817. (Amended) The oligo- or polydeoxyribonucleotide of claims 596 or 677, wherein said Sig is covalently attached to said at least one phosphate through a chemical linkage comprising a polypeptide [~~or a protein~~].



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819. (Amended) The oligo- or polydeoxyribonucleotide of claim 817, wherein said polypeptide [~~or protein~~] is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

820. (Amended) The oligo- or polynucleotide of claims 617 or 697, wherein said Sig is covalently attached to PM via a chemical linkage comprising a polypeptide [~~or a protein~~].

822. (Amended) The oligo- or polydeoxyribonucleotide of claim 820, wherein said polypeptide [~~or protein~~] is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

823. (Amended) The oligo- or polynucleotide of claims 637 or 716, wherein said Sig is covalently attached to said at least one phosphate through a chemical linkage comprising a polypeptide [~~or a protein~~].

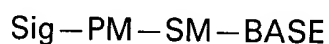
825. (Amended) The oligo- or polydeoxyribonucleotide of claim 824, wherein said polypeptide [~~or protein~~] is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

\* \* \* \* \*

ENGELHARDT ET AL., U.S. PAT. APPL. SER. NO. 08/479,997  
CONSOLIDATED CLAIMS 576, 578-596, 598-617, 619-637, 639-658, 660-677,  
679-697, 699-716, 718-736, 738-755, 757-775, 777-794 & 796-825

[Pending Claims Following Entry of Applicants' October 28, 2002 Amendment  
Under 37 C.F.R. §1.116 (In Response To October 8, 2002 Office Action)]

576. An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the formula

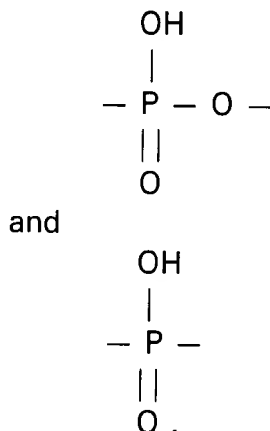


wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a base moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM directly or through a chemical linkage, said Sig comprising a non-polypeptide, non-radioactive label moiety which can be directly or indirectly detected when attached to PM or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

~~577. (Canceled) The oligo- or polydeoxyribonucleotide of claim 576, wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

578. The oligo- or polydeoxyribonucleotide of claim 576, wherein said Sig moiety comprises at least three carbon atoms.

579. The oligo- or polydeoxyribonucleotide of claim 576, wherein said covalent attachment is selected from the group consisting of

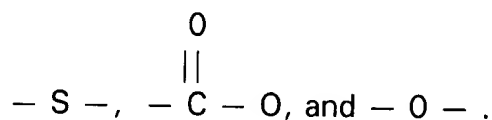
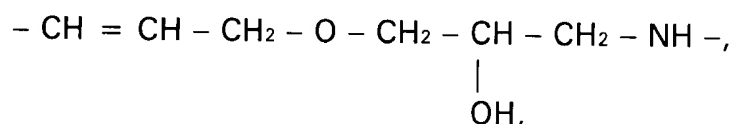
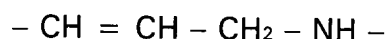


580. The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

581. (Amended) The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage comprises a -CH<sub>2</sub>NH- moiety.

582. The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage comprises an allylamine group.

583. (Amended) The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage comprises any of the moieties:



584. The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

585. The oligo- or polydeoxyribonucleotide of claim 576, wherein said PM is monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached to said PM through a phosphorus atom or phosphate oxygen.

586. The oligo- or polydeoxyribonucleotide of claim 576, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

587. The oligo- or polydeoxyribonucleotide of claim 586, wherein said electron dense component comprises ferritin.

588. The oligo- or polydeoxyribonucleotide of claim 586, wherein said magnetic component comprises magnetic oxide.

589. The oligo- or polydeoxyribonucleotide of claim 588, wherein said magnetic oxide comprises ferric oxide.

590. The oligo- or polydeoxyribonucleotide of claim 586, wherein said metal-containing component is catalytic.

591. The oligo- or polydeoxyribonucleotide of claim 586, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

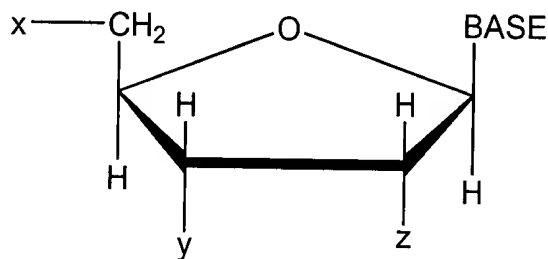
592. The oligo- or polydeoxyribonucleotide of claim 576, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

593. The oligo- or polydeoxyribonucleotide of claim 592, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.

594. The oligo- or polydeoxyribonucleotide of claim 592, wherein the sugar moiety of said terminal nucleotide has oxygen atoms at each of the 2' and 3' positions thereof.

595. The oligo- or polydeoxyribonucleotide of claim 576, comprising at least one ribonucleotide.

596. An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

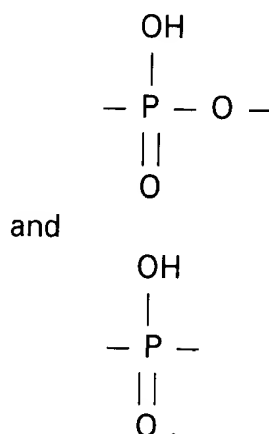
wherein Sig is covalently attached directly or through a chemical linkage to at least one phosphate selected from the group consisting of x, y, z, and a combination thereof, said Sig comprising a non-polypeptide, non-radioactive label moiety which

can be directly or indirectly detected when so attached to said phosphate or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

~~597. (Canceled) The oligo- or polydeoxyribonucleotide of claim 596, wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

598. The oligo- or polydeoxyribonucleotide of claim 596, wherein said Sig moiety comprises at least three carbon atoms.

599. The oligo- or polydeoxyribonucleotide of claim 596, wherein said covalent attachment is selected from the group consisting of

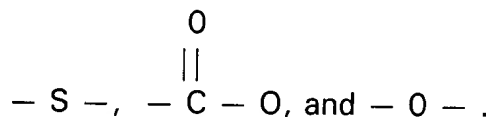
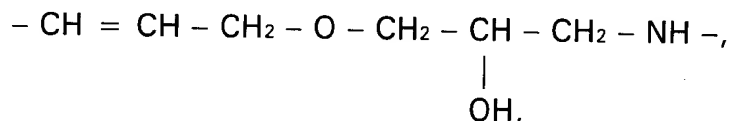


600. The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

601. (Amended) The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage comprises a -CH<sub>2</sub>NH- moiety.

602. The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage comprises an allylamine group.

603. (Amended) The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage comprises any of the moieties:



604. The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.



605. The oligo- or polydeoxyribonucleotide of claim 596, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and said Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or phosphate oxygen.

606. The oligo- or polydeoxyribonucleotide of claim 596, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

607. The oligo- or polydeoxyribonucleotide of claim 606, wherein said electron dense component comprises ferritin.

608. The oligo- or polydeoxyribonucleotide of claim 606, wherein said magnetic component comprises magnetic oxide.

609. The oligo- or polydeoxyribonucleotide of claim 608, wherein said magnetic oxide comprises ferric oxide.

610. The oligo- or polydeoxyribonucleotide of claim 606, wherein said metal-containing component is catalytic.

611. The oligo- or polydeoxyribonucleotide of claim 606, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

612. The oligo- or polydeoxyribonucleotide of claim 596, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

613. The oligo- or polydeoxyribonucleotide of claim 612, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.

614. The oligo- or polydeoxyribonucleotide of claim 612, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.

615. The oligo- or polydeoxyribonucleotide of claim 596, comprising at least one ribonucleotide.

Chemical structure of a branched nucleic acid polymer. The main chain consists of a phosphate group (HO-P(=O)(OH)-) linked to a deoxyribose sugar (H-C<sub>2</sub>H, H-C<sub>3</sub>H, H-C<sub>4</sub>H, CH<sub>2</sub>-O), which is linked to a phosphate group (O-P(=O)(OH)-). This unit is enclosed in brackets with a subscript 'm'. The side chain branches off from the 3' carbon of the first sugar in the main chain. It consists of a phosphate group (O-P(=O)(OH)-) linked to a deoxyribose sugar (H-C<sub>2</sub>H, H-C<sub>3</sub>H, H-C<sub>4</sub>H, CH<sub>2</sub>-O), which is linked to a phosphate group (O-P(=O)(OH)-). This unit is enclosed in brackets with a subscript 'n'. The base is labeled 'BASE'.

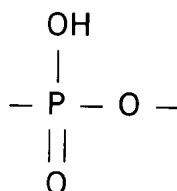
wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM,

and Sig being covalently attached to PM directly or via a chemical linkage, said Sig comprising a non-polypeptide, non-radioactive label moiety which can be directly or indirectly detected when attached to PM or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide, and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

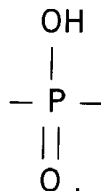
~~618. (Canceled) The oligo- or polynucleotide of claim 617, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

619. The oligo- or polynucleotide of claim 617, wherein said Sig moiety comprises at least three carbon atoms.

620. The oligo- or polynucleotide of claim 617, wherein said covalent attachment is selected from the group consisting of



and

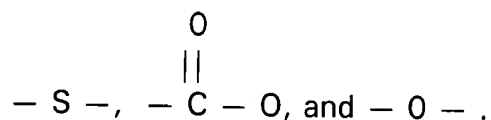
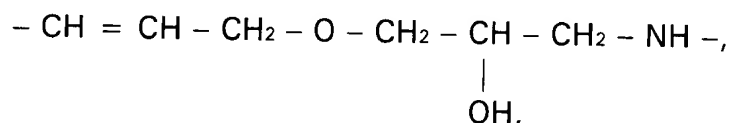
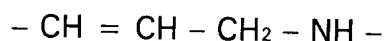


621. The oligo- or polynucleotide of claim 617, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

622. (Amended) The oligo- or polynucleotide of claim 617, wherein said chemical linkage comprises a  $-\text{CH}_2\text{NH}-$  moiety.

623. The oligo- or polynucleotide of claim 617, wherein said chemical linkage comprises an allylamine group.

624. (Amended) The oligo- or polynucleotide of claim 617, wherein said chemical linkage comprises any of the moieties:



625. The oligo- or polynucleotide of claim 617, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

626. The oligo- or polynucleotide of claim 617, wherein said PM is a monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached to said PM through a phosphorus atom or a phosphate oxygen.

627. The oligo- or polynucleotide of claim 617, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

628. The oligo- or polynucleotide of claim 627, wherein said electron dense component comprises ferritin.

629. The oligo- or polynucleotide of claim 627, wherein said magnetic component comprises magnetic oxide.

630. The oligo- or polynucleotide of claim 629, wherein said magnetic oxide comprises ferric oxide.

631. The oligo- or polynucleotide of claim 627, wherein said metal-containing component is catalytic.

632. The oligo- or polynucleotide of claim 627, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

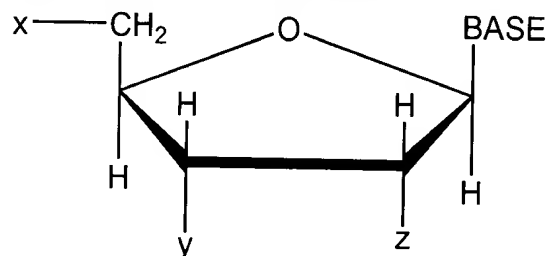
633. The oligo- or polynucleotide of claim 617, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polynucleotide.

634. The oligo- or polynucleotide of claim 633, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.

635. The oligo- or polynucleotide of claim 633, wherein the sugar moiety of said terminal nucleotide has an oxygen atom at each of the 2' and 3' positions thereof.

636. The oligo- or polynucleotide of claim 617, comprising at least one deoxyribonucleotide.

637. An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

wherein Sig is covalently attached directly or through a chemical linkage to at least one phosphate selected from the group consisting of x, y and z, and a combination thereof, said Sig comprising a non-polypeptide, non-radioactive label moiety which can be directly or indirectly detected when so attached to said phosphate or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide and

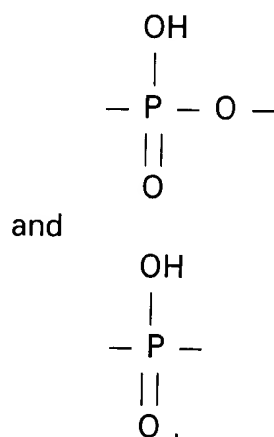


when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

~~638. (Canceled) The oligo- or polynucleotide of claim 637, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

639. The oligo- or polynucleotide of claim 637, wherein said Sig moiety comprises at least three carbon atoms.

640. The oligo- or polynucleotide of claim 637, wherein said covalent attachment is selected from the group consisting of

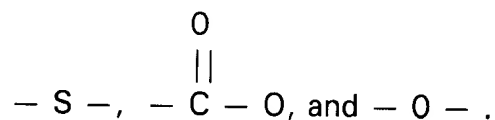
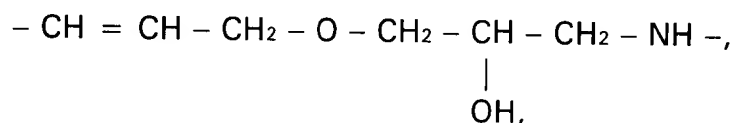
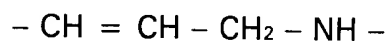


641. The oligo- or polynucleotide of claim 637, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

642. (Amended) The oligo- or polynucleotide of claim 637, wherein said chemical linkage comprises -CH<sub>2</sub>NH- moiety.

643. The oligo- or polynucleotide of claim 637, wherein said chemical linkage comprises an allylamine group.

644. (Amended) The oligo- or polynucleotide of claim 637, wherein said chemical linkage comprises any of the moieties:



645. The oligo- or polynucleotide of claim 637, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

646. The oligo- or polynucleotide of claim 637, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or a phosphate oxygen.

647. The oligo- or polynucleotide of claim 637, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

648. The oligo- or polynucleotide of claim 647, wherein said electron dense component comprises ferritin.

649. The oligo- or polynucleotide of claim 647, wherein said magnetic component comprises magnetic oxide.

650. The oligo- or polynucleotide of claim 649, wherein said magnetic oxide comprises ferric oxide.

651. The oligo- or polynucleotide of claim 647, wherein said metal-containing component is catalytic.

652. The oligo- or polynucleotide of claim 647, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

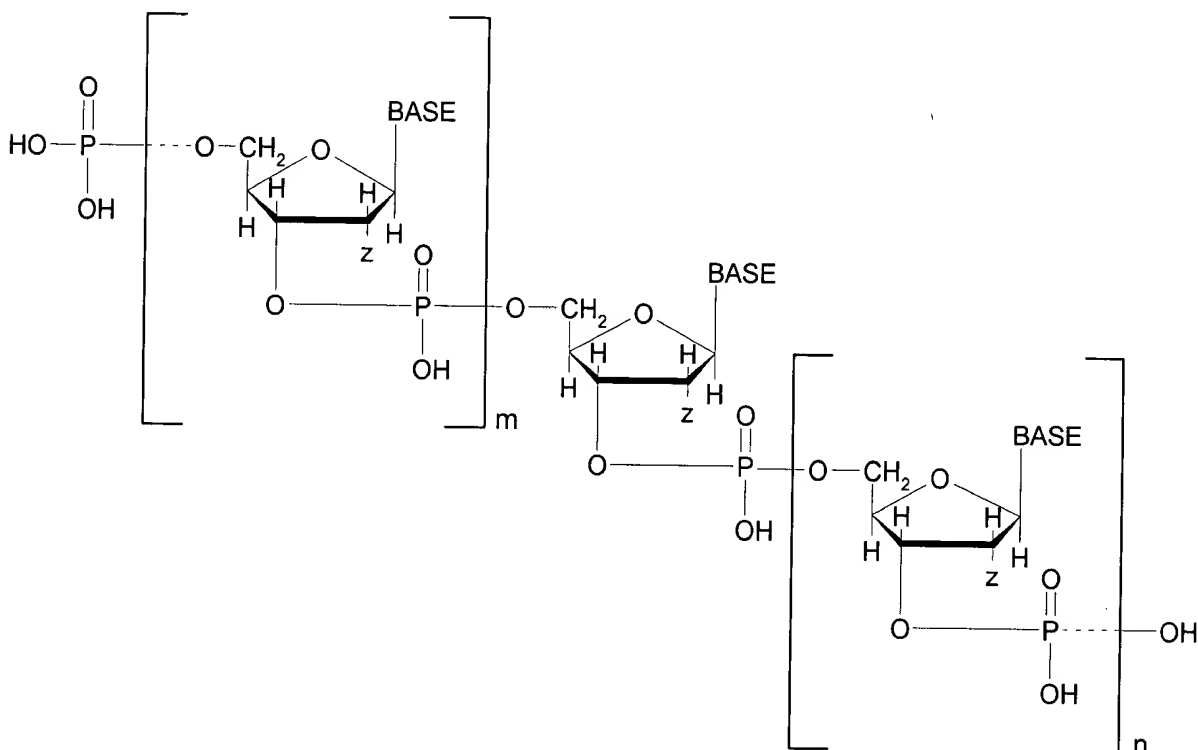
653. The oligo- or polynucleotide of claim 637, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polynucleotide.

654. The oligo- or polynucleotide of claim 653, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.

655. The oligo- or polynucleotide of claim 653, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.

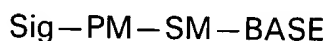
656. The oligo- or polynucleotide of claim 637, comprising at least one deoxyribonucleotide.

657. The oligo- or polynucleotide of claim 637, having the structural formula:



wherein m and n represent integers from 0 up to about 100,000, and wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula.

658. An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the formula



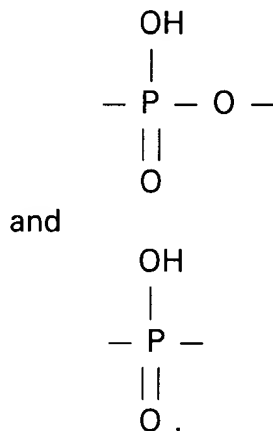
wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a base moiety selected from the group consisting of a pyrimidine, a purine and a

deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM directly or through a chemical linkage, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to PM or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, and wherein Sig comprises biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

~~659. (Canceled) The oligo- or polydeoxyribonucleotide of claim 658, wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

660. The oligo- or polydeoxyribonucleotide of claim 658, wherein said Sig moiety comprises at least three carbon atoms.

661. The oligo- or polydeoxyribonucleotide of claim 658, wherein said covalent attachment is selected from the group consisting of

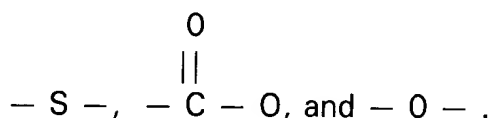
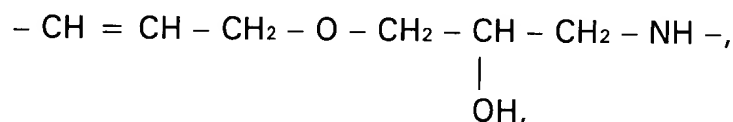
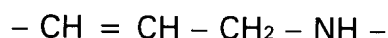


662. The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

663. (Amended) The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage comprises a -CH<sub>2</sub>NH- moiety.

664. The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage comprises an allylamine group.

665. (Amended) The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage comprises any of the moieties:



666. The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

667. The oligo- or polydeoxyribonucleotide of claim 658, wherein said PM is monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached to said PM through a phosphorus atom or phosphate oxygen.

668. The oligo- or polydeoxyribonucleotide of claim 658, wherein said electron dense component comprises ferritin.

669. The oligo- or polydeoxyribonucleotide of claim 658, wherein said magnetic component comprises magnetic oxide.

670. The oligo- or polydeoxyribonucleotide of claim 658, wherein said magnetic oxide comprises ferric oxide.



671. The oligo- or polydeoxyribonucleotide of claim 658, wherein said metal-containing component is catalytic.

672. The oligo- or polydeoxyribonucleotide of claim 658, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

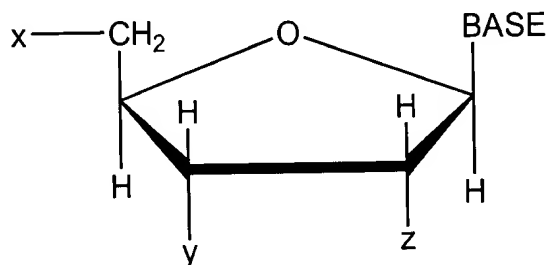
673. The oligo- or polydeoxyribonucleotide of claim 658, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

674. The oligo- or polydeoxyribonucleotide of claim 673, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.

675. The oligo- or polydeoxyribonucleotide of claim 673, wherein the sugar moiety of said terminal nucleotide has oxygen atoms at each of the 2' and 3' positions thereof.

676. The oligo- or polydeoxyribonucleotide of claim 658, comprising at least one ribonucleotide.

677. An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of  $\text{H}-$ ,  $\text{HO}-$ , a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of  $\text{H}-$ ,  $\text{HO}-$ , a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of  $\text{H}-$ ,  $\text{HO}-$ , a mono-phosphate, a di-phosphate and a tri-phosphate; and

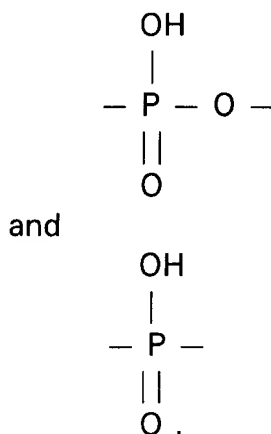
wherein Sig is covalently attached directly or through a chemical linkage to at least one phosphate selected from the group consisting of x, y, z, and a combination thereof, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when so attached to said phosphate or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, wherein Sig comprises biotin,

iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

~~678. (Canceled) The oligo- or polydeoxyribonucleotide of claim 677, wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

679. The oligo- or polydeoxyribonucleotide of claim 677, wherein said Sig moiety comprises at least three carbon atoms.

680. The oligo- or polydeoxyribonucleotide of claim 677, wherein said covalent attachment is selected from the group consisting of

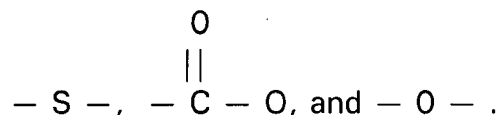
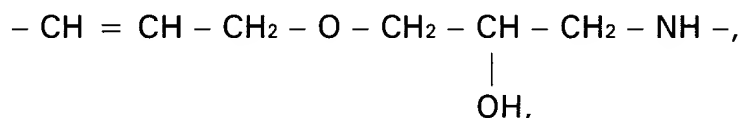
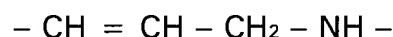


681. The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

682. (Amended) The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage comprises a  $-\text{CH}_2\text{NH}-$  moiety.

683. The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage comprises an allylamine group.

684. (Amended) The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage comprises any of the moieties:



685. The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

686. The oligo- or polydeoxyribonucleotide of claim 677, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and said Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or phosphate oxygen.

687. The oligo- or polydeoxyribonucleotide of claim 677, wherein said electron dense component comprises ferritin.

688. The oligo- or polydeoxyribonucleotide of claim 677, wherein said magnetic component comprises magnetic oxide.

689. The oligo- or polydeoxyribonucleotide of claim 688, wherein said magnetic oxide comprises ferric oxide.

690. The oligo- or polydeoxyribonucleotide of claim 677, wherein said metal-containing component is catalytic.

691. The oligo- or polydeoxyribonucleotide of claim 677, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

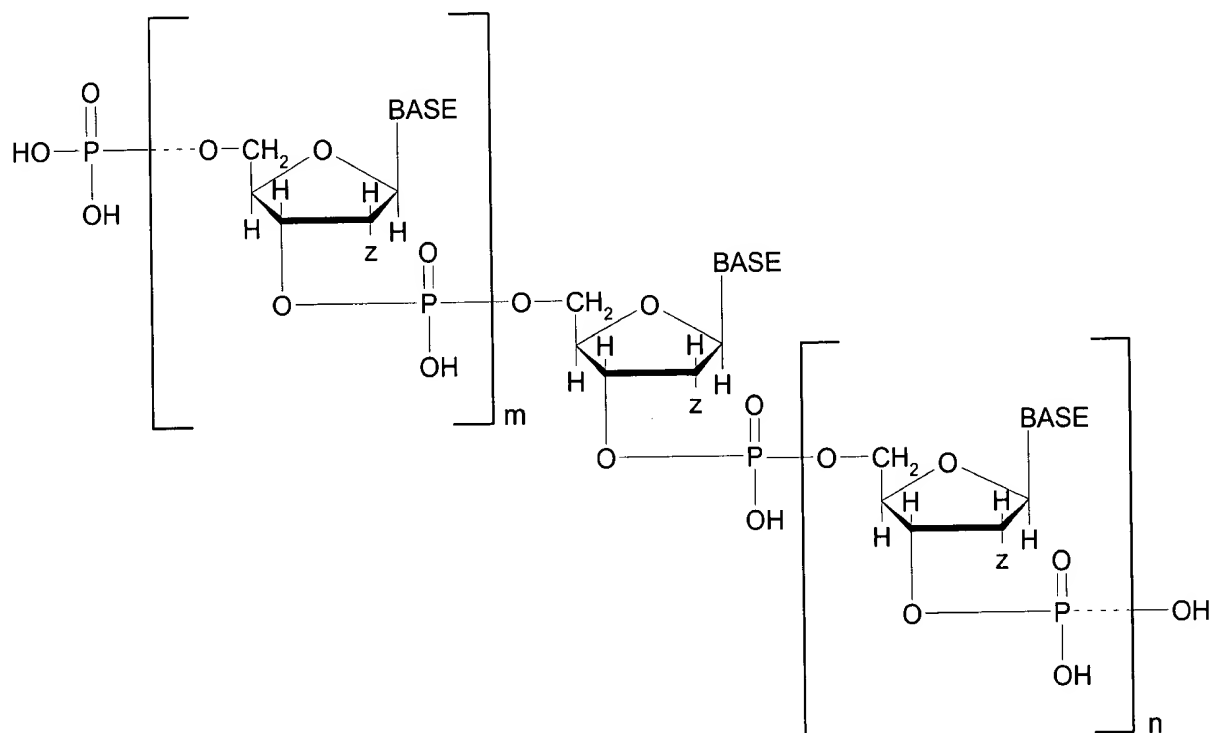
692. The oligo- or polydeoxyribonucleotide of claim 677, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

693. The oligo- or polydeoxyribonucleotide of claim 692, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.

694. The oligo- or polydeoxyribonucleotide of claim 692, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.

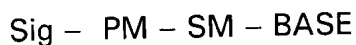
695. The oligo- or polydeoxyribonucleotide of claim 677, comprising at least one ribonucleotide.

696. The oligo- or polydexoyribonucleotide of claim 677, having the structural formula:



wherein  $m$  and  $n$  represent integers from 0 up to about 100,000, and wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula.

697. An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the formula

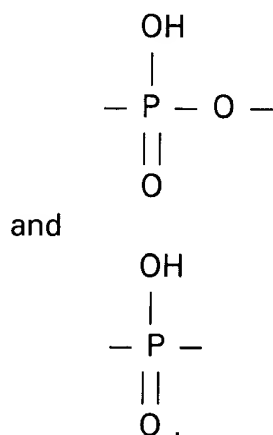


wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM directly or via a chemical linkage, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to PM or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide, and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide, wherein Sig comprises biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

~~698. (Canceled) The oligo- or polynucleotide of claim 697, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

699. The oligo- or polynucleotide of claim 697, wherein said Sig moiety comprises at least three carbon atoms.

700. The oligo- or polynucleotide of claim 697, wherein said covalent attachment is selected from the group consisting of



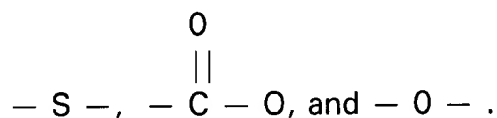
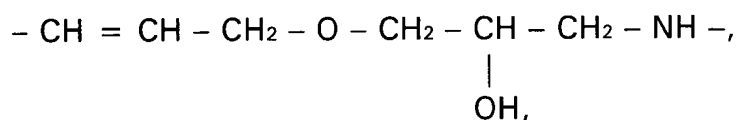
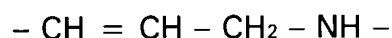
701. The oligo- or polynucleotide of claim 697, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

702. (Amended) The oligo- or polynucleotide of claim 697, wherein said chemical linkage comprises a -CH<sub>2</sub>NH- moiety.

703. The oligo- or polynucleotide of claim 697, wherein said chemical linkage comprises an allylamine group.



704. (Amended) The oligo- or polynucleotide of claim 697, wherein said chemical linkage comprises any of the moieties:



705. The oligo- or polynucleotide of claim 697, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

706. The oligo- or polynucleotide of claim 697, wherein said PM is a monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached to said PM through a phosphorus atom or a phosphate oxygen.

707. The oligo- or polynucleotide of claim 697, wherein said electron dense component comprises ferritin.

708. The oligo- or polynucleotide of claim 697, wherein said magnetic component comprises magnetic oxide.

709. The oligo- or polynucleotide of claim 708, wherein said magnetic oxide comprises ferric oxide.

710. The oligo- or polynucleotide of claim 697, wherein said metal-containing component is catalytic.

711. The oligo- or polynucleotide of claim 697, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

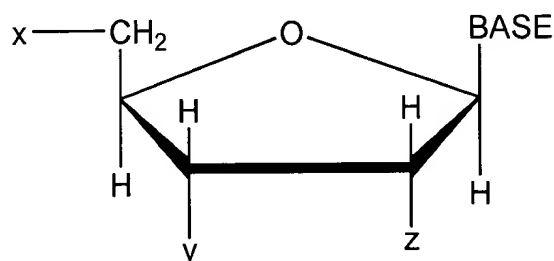
712. The oligo- or polynucleotide of claim 697, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polynucleotide.

713. The oligo- or polynucleotide of claim 712, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.

714. The oligo- or polynucleotide of claim 712, wherein the sugar moiety of said terminal nucleotide has an oxygen atom at each of the 2' and 3' positions thereof.

715. The oligo- or polynucleotide of claim 697, comprising at least one deoxyribonucleotide.

716. An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

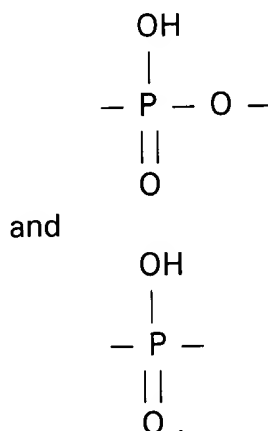
wherein Sig is covalently attached directly or through a chemical linkage to at least one phosphate selected from the group consisting of x, y and z, and a combination thereof, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when so attached to said phosphate or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an

oligoribonucleotide or a polyribonucleotide and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide, wherein Sig comprises biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

~~717. (Canceled) The oligo- or polynucleotide of claim 716, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

718. The oligo- or polynucleotide of claim 716, wherein said Sig moiety comprises at least three carbon atoms.

719. The oligo- or polynucleotide of claim 716, wherein said covalent attachment is selected from the group consisting of

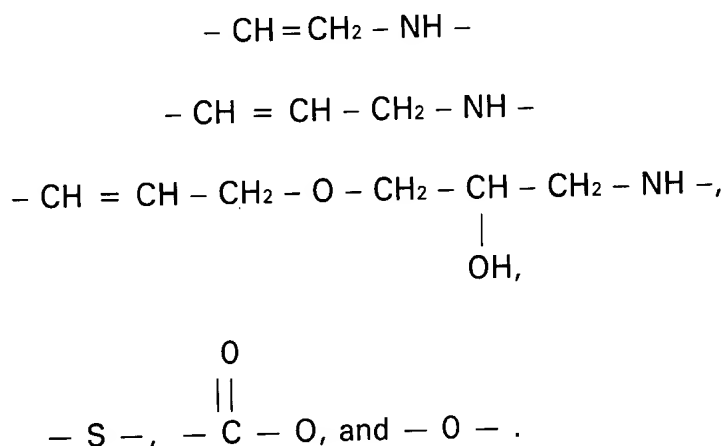


720. The oligo- or polynucleotide of claim 716, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

721. (Amended) The oligo- or polynucleotide of claim 716, wherein said chemical linkage comprises a  $-\text{CH}_2\text{NH}-$  moiety.

722. The oligo- or polynucleotide of claim 716, wherein said chemical linkage comprises an allylamine group.

723. (Amended) The oligo- or polynucleotide of claim 716, wherein said chemical linkage comprises any of the moieties:



724. The oligo- or polynucleotide of claim 716, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

725. The oligo- or polynucleotide of claim 716, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or a phosphate oxygen.

726. The oligo- or polynucleotide of claim 716, wherein said electron dense component comprises ferritin.

727. The oligo- or polynucleotide of claim 716, wherein said magnetic component comprises magnetic oxide.

728. The oligo- or polynucleotide of claim 727, wherein said magnetic oxide comprises ferric oxide.

729. The oligo- or polynucleotide of claim 716, wherein said metal-containing component is catalytic.

730. The oligo- or polynucleotide of claim 716, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

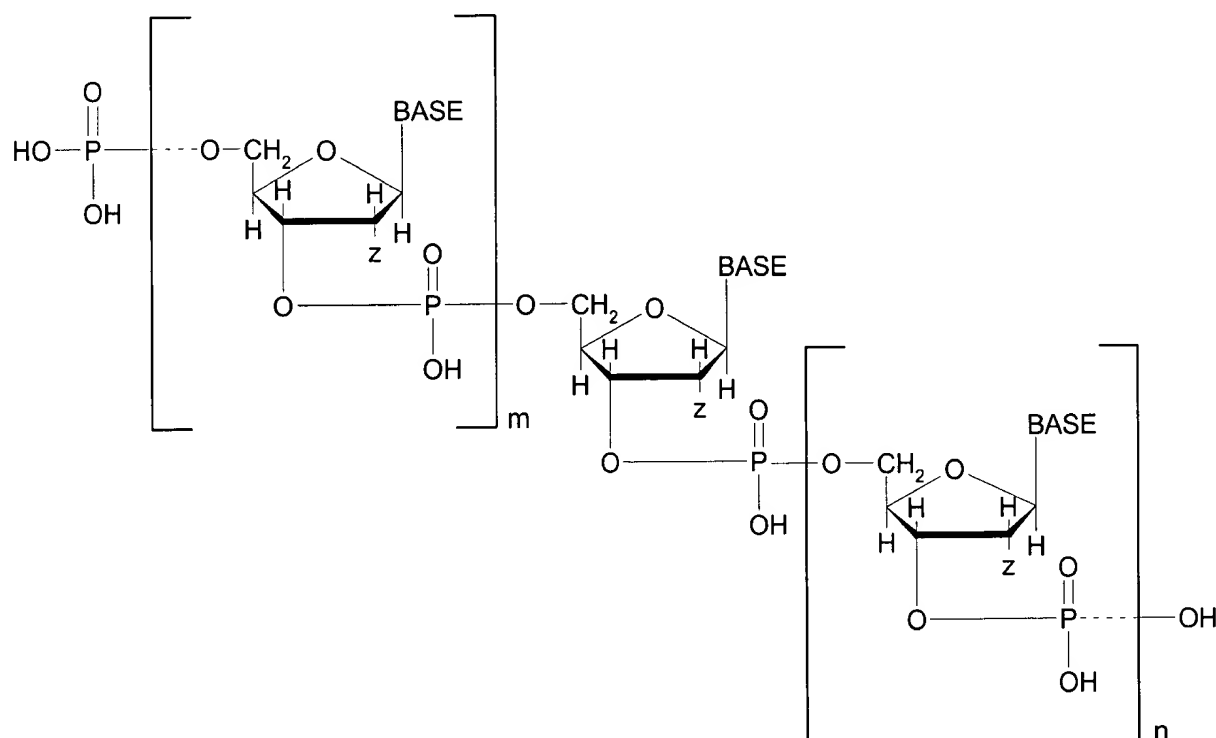
731. The oligo- or polynucleotide of claim 716, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polynucleotide.

732. The oligo- or polynucleotide of claim 731, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.

733. The oligo- or polynucleotide of claim 731, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.

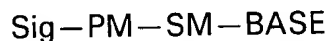
734. The oligo- or polynucleotide of claim 716, comprising at least one deoxyribonucleotide.

735. The oligo- or polynucleotide of claim 716, having the structural formula:



wherein m and n represent integers from 0 up to about 100,000, and wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula.

736. (Amended) An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the formula



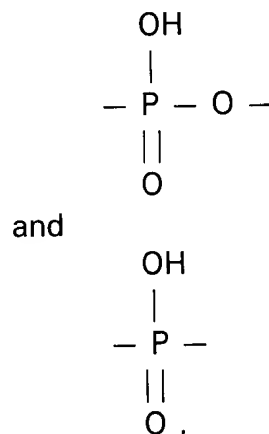
wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a base moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM through a chemical linkage comprising a polypeptide, and said Sig comprising a non-radioactive label moiety which can be directly detected when indirectly attached to PM through said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

~~737. (Canceled) The oligo- or polydeoxyribonucleotide of claim 736, wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

738. The oligo- or polydeoxyribonucleotide of claim 736, wherein said Sig moiety comprises at least three carbon atoms.



739. The oligo- or polydeoxyribonucleotide of claim 736, wherein said covalent attachment is selected from the group consisting of



740. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

741. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said PM is monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached via said polypeptide chemical linkage to said PM through a phosphorus atom or phosphate oxygen.

742. The oligo- or polydeoxyribonucleotide of claim 736, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

743. The oligo- or polydeoxyribonucleotide of claim 742, wherein said electron dense component comprises ferritin.

744. The oligo- or polydeoxyribonucleotide of claim 742, wherein said magnetic component comprises magnetic oxide.

745. The oligo- or polydeoxyribonucleotide of claim 744, wherein said magnetic oxide comprises ferric oxide.

746. The oligo- or polydeoxyribonucleotide of claim 742, wherein said metal-containing component is catalytic.

747. The oligo- or polydeoxyribonucleotide of claim 742, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

748. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said oligo- or polydeoxyribonucleotide is terminally ligated or attached to said polypeptide chemical linkage.

749. The oligo- or polydeoxyribonucleotide of claim 736, wherein said polypeptide comprises polylysine.

750. The oligo- or polydeoxyribonucleotide of claim 736, wherein said polypeptide is selected from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

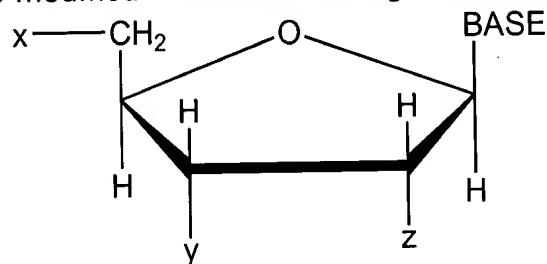
751. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said Sig moiety is attached via said polypeptide chemical linkage to a phosphate moiety in a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

752. The oligo- or polydeoxyribonucleotide of claim 751, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.

753. The oligo- or polydeoxyribonucleotide of claim 751, wherein the sugar moiety of said terminal nucleotide has oxygen atoms at each of the 2' and 3' positions thereof.

754. The oligo- or polydeoxyribonucleotide of claim 736, comprising at least one ribonucleotide.

755. (Amended) An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1' position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein  $x$  is selected from the group consisting of  $\text{H}-$ ,  $\text{HO}-$ , a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein  $y$  is selected from the group consisting of  $\text{H}-$ ,  $\text{HO}-$ , a mono-phosphate, a di-phosphate and a tri-phosphate;

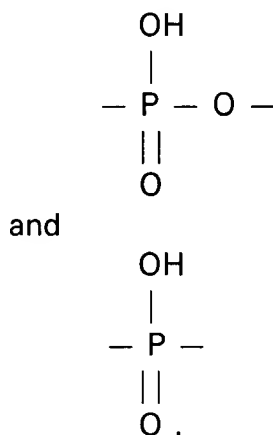
wherein  $z$  is selected from the group consisting of  $\text{H}-$ ,  $\text{HO}-$ , a mono-phosphate, a di-phosphate and a tri-phosphate; and

wherein Sig is covalently attached through a chemical linkage to at least one phosphate selected from the group consisting of  $x$ ,  $y$ ,  $z$ , and a combination thereof, said chemical linkage comprising a polypeptide, and said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to said phosphate via said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polydeoxynucleotide or when said oligo- or polydeoxynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

~~756. (Canceled) The oligo- or polydeoxyribonucleotide of claim 755, wherein said Sig is or renders the modified nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

757. The oligo- or polydeoxyribonucleotide of claim 755, wherein said Sig moiety comprises at least three carbon atoms.

758. The oligo- or polydeoxyribonucleotide of claim 755, wherein said covalent attachment is selected from the group consisting of



759. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

760. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and said Sig moiety is covalently attached via said polypeptide chemical linkage to either or both of said x and y through a phosphorus atom or phosphate oxygen.

761. The oligo- or polydeoxyribonucleotide of claim 755, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component, or a combination of any of the foregoing.

762. The oligo- or polydeoxyribonucleotide of claim 761, wherein said electron dense component comprises ferritin.

763. The oligo- or polydeoxyribonucleotide of claim 761, wherein said magnetic component comprises magnetic oxide.

764. The oligo- or polydeoxyribonucleotide of claim 763, wherein said magnetic oxide comprises ferric oxide.

765. The oligo- or polydeoxyribonucleotide of claim 761, wherein said metal-containing component is catalytic.

766. The oligo- or polydeoxyribonucleotide of claim 761, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

767. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said oligo- or polydeoxyribonucleotide is terminally ligated or attached to said polypeptide chemical linkage.

768. The composition of claim 755, wherein said polypeptide comprises polylysine.

769. The composition of claim 755, wherein said polypeptide is selected from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

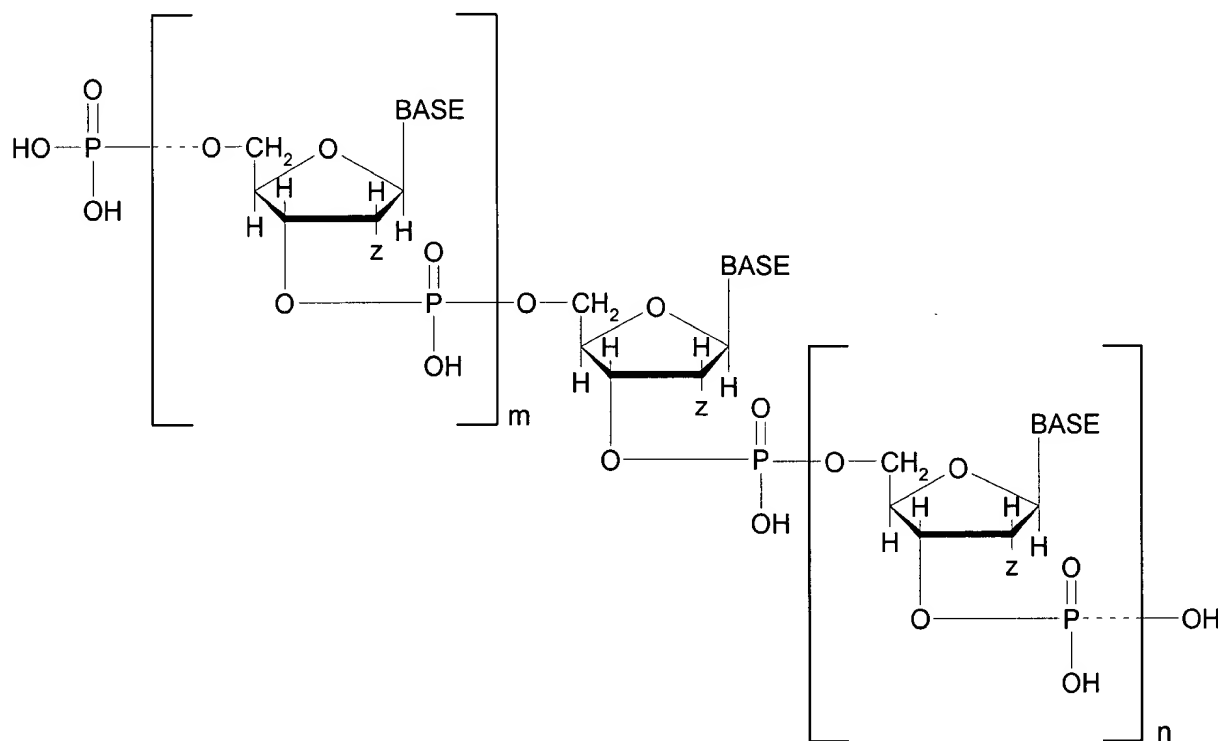
770. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said Sig moiety is attached via said polypeptide chemical linkage to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

771. The oligo- or polydeoxyribonucleotide of claim 770, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.

772. The oligo- or polydeoxyribonucleotide of claim 770, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.

773. The oligo- or polydeoxyribonucleotide of claim 755, comprising at least one ribonucleotide.

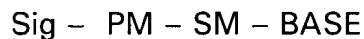
774. The oligo- or polydeoxyribonucleotide of claim 755, having the structural formula:



wherein m and n represent integers from 0 up to about 100,000, and wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula.



775. (Amended) An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the formula

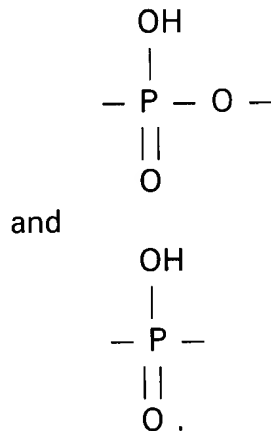


wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM via a chemical linkage comprising a polypeptide, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to PM via said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide, and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

~~776. (Canceled) The oligo- or polynucleotide of claim 775, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

777. The oligo- or polynucleotide of claim 775, wherein said Sig moiety comprises at least three carbon atoms.

778. The oligo- or polynucleotide of claim 775, wherein said covalent attachment is selected from the group consisting of



779. (Amended) The oligo- or polynucleotide of claim 775, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

780. (Amended) The oligo- or polynucleotide of claim 775, wherein said PM is a monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached via said polypeptide chemical linkage to said PM through a phosphorus atom or a phosphate oxygen.

781. The oligo- or polynucleotide of claim 775, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

782. The oligo- or polynucleotide of claim 781, wherein said electron dense component comprises ferritin.

783. The oligo- or polynucleotide of claim 781, wherein said magnetic component comprises magnetic oxide.

784. The oligo- or polynucleotide of claim 783, wherein said magnetic oxide comprises ferric oxide.

785. The oligo- or polynucleotide of claim 781, wherein said metal-containing component is catalytic.

786. The oligo- or polynucleotide of claim 781, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

787. (Amended) The oligo- or polynucleotide of claim 775, wherein said oligo- or polynucleotide is terminally ligated or attached to said polypeptide chemical linkage.

788. The oligo- or polynucleotide of claim 775, wherein said polypeptide comprises polylysine.

789. The oligo- or polynucleotide of claim 775, wherein said polypeptide is selected from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

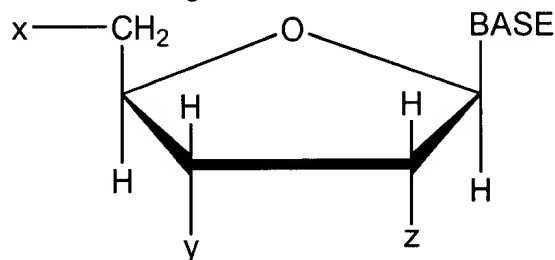
790. (Amended) The oligo- or polynucleotide of claim 775, wherein said Sig moiety is attached via said polypeptide chemical linkage to a terminal nucleotide in said oligo- or polynucleotide.

791. The oligo- or polynucleotide of claim 790, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.

792. The oligo- or polynucleotide of claim 790, wherein the sugar moiety of said terminal nucleotide has an oxygen atom at each of the 2' and 3' positions thereof.

793. The oligo- or polynucleotide of claim 775, comprising at least one deoxyribonucleotide.

794. (Amended) An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

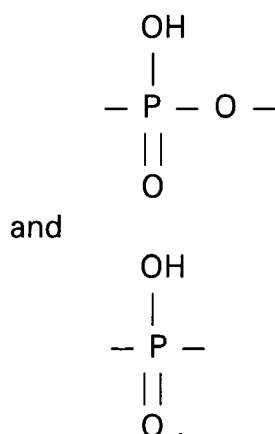
wherein Sig is covalently attached through a chemical linkage to at least one phosphate selected from the group consisting of x, y and z, and a combination thereof, said chemical linkage comprising a polypeptide, and said Sig comprising a non-radioactive label moiety which can be directly detected when attached to said phosphate via said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a

polyribonucleotide and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

~~795. (Canceled) The oligo- or polynucleotide of claim 794, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

796. The oligo- or polynucleotide of claim 794, wherein said Sig moiety comprises at least three carbon atoms.

797. The oligo- or polynucleotide of claim 794, wherein said covalent attachment is selected from the group consisting of



798. (Amended) The oligo- or polynucleotide of claim 794, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

799. (Amended) The oligo- or polynucleotide of claim 794, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or a phosphate oxygen.

800. The oligo- or polynucleotide of claim 794, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

801. The oligo- or polynucleotide of claim 800, wherein said electron dense component comprises ferritin.

802. The oligo- or polynucleotide of claim 800, wherein said magnetic component comprises magnetic oxide.

803. The oligo- or polynucleotide of claim 802, wherein said magnetic oxide comprises ferric oxide.

804. The oligo- or polynucleotide of claim 800, wherein said metal-containing component is catalytic.

805. The oligo- or polynucleotide of claim 800, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

806. (Amended) The oligo- or polynucleotide of claim 794, wherein said oligo- or polynucleotide is terminally ligated or attached to said polypeptide chemical linkage.

807. The oligo- or polynucleotide of claim 794, wherein said polypeptide comprises polylysine.

808. The oligo- or polynucleotide of claim 794, wherein said polypeptide is selected from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

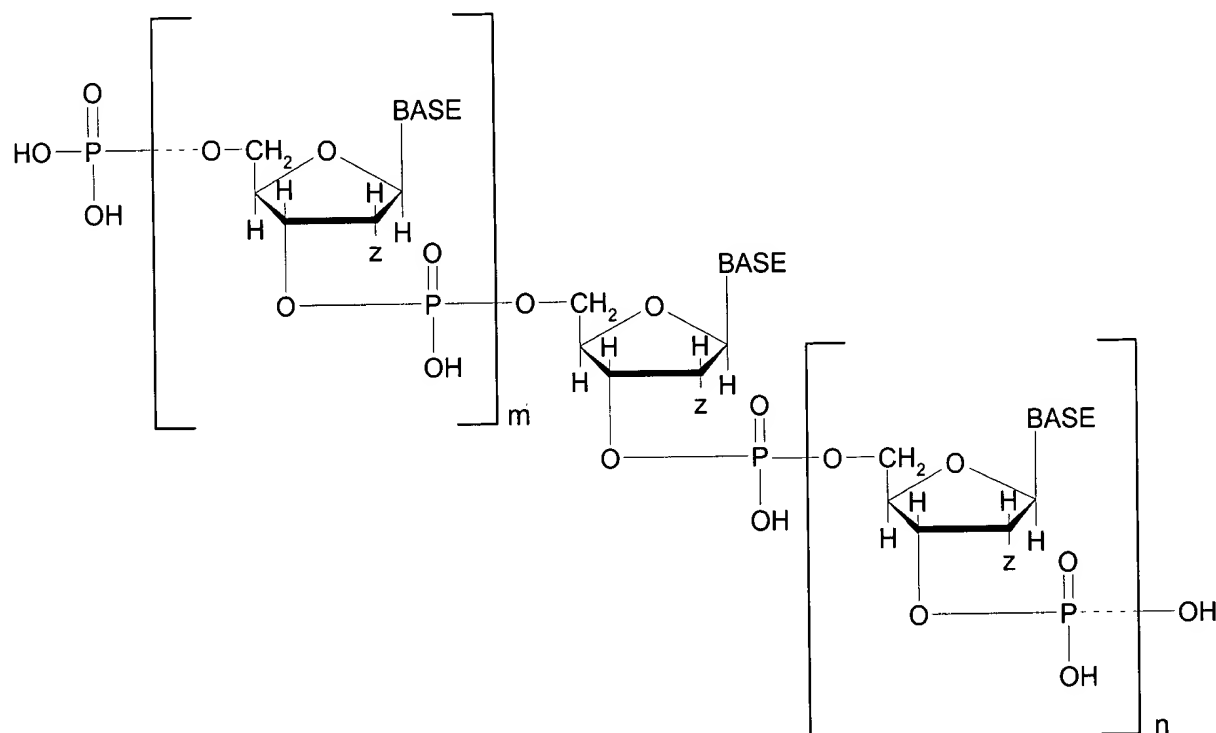
809. (Amended) The oligo- or polynucleotide of claim 794, wherein said Sig moiety is attached via said polypeptide chemical linkage to a terminal nucleotide in said oligo- or polynucleotide.

810. The oligo- or polynucleotide of claim 809, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.

811. The oligo- or polynucleotide of claim 809, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.



813. The oligo- or polynucleotide of claim 794, having the structural formula:



814. (Amended) The oligo- or polydeoxyribonucleotide of claims 576 or 658, wherein said Sig is covalently attached to PM through a chemical linkage comprising a polypeptide.

815. The oligo- or polydeoxyribonucleotide of claim 814, wherein said polypeptide comprises polylysine.

816. (Amended) The oligo- or polydeoxyribonucleotide of claim 814, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

817. (Amended) The oligo- or polydeoxyribonucleotide of claims 596 or 677, wherein said Sig is covalently attached to said at least one phosphate through a chemical linkage comprising a polypeptide.

818. The oligo- or polydeoxyribonucleotide of claim 817, wherein said polypeptide comprises polylysine.

819. (Amended) The oligo- or polydeoxyribonucleotide of claim 817, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

820. (Amended) The oligo- or polynucleotide of claims 617 or 697, wherein said Sig is covalently attached to PM via a chemical linkage comprising a polypeptide.

821. The oligo- or polydeoxyribonucleotide of claim 820, wherein said polypeptide comprises polylysine.

822. (Amended) The oligo- or polydeoxyribonucleotide of claim 820, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

823. (Amended) The oligo- or polynucleotide of claims 637 or 716, wherein said Sig is covalently attached to said at least one phosphate through a chemical linkage comprising a polypeptide.

824. The oligo- or polydeoxyribonucleotide of claim 823, wherein said polypeptide comprises polylysine.

825. (Amended) The oligo- or polydeoxyribonucleotide of claim 824, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

\* \* \* \* \*

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant(s):	Engelhardt et al.	)	
		)	
Serial No.:	08/479,997	)	Group Art Unit: 1656
		)	
Filed:	June 7, 1995	)	Ex'r: Alexander H. Spiegler
		)	
For:	<b>OLIGO- OR POLYNUCLEOTIDES</b>	)	
	<b>COMPRISING PHOSPHATE MOIETY</b>	)	
	<b>LABELED NUCLEOTIDES</b>	)	
	(As Previously Amended)	)	

St. Louis, Missouri 63124

Director of Patents and Trademarks  
Washington, D.C. 20231

**SUPPLEMENTAL DECLARATION OF DR. CHARLES W. PARKER**

I, Charles W. Parker, hereby declare as follows:

1. I am the same Charles W. Parker who previously signed a Declaration on May 21, 2002 for submission in the above-identified application [United States Patent Application Serial No. 08/479,997, filed on June 7, 1995, for "Oligo- or Polynucleotides Comprising Phosphate Moiety Labeled Nucleotides," Dean L. Engelhardt et al., inventors]. I have been informed by Enzo Biochem, Inc.'s attorney that my previous Declaration (hereinafter "May 2002 Declaration") was filed with the United States Patent and Trademark Office on May 28, 2002 as part of a document titled "Amendment Under 37 C.F.R. §1.115." I continue to hold the position of Professor *Emeritus* of Medicine, Department of Microbiology and Immunology at Washington University School of Medicine (WUSM), St. Louis, Missouri. I also continue to be active at WUSM. My professional experience, education, research experience, awards, honors, publications and other

accomplishments and activities were listed on my *curriculum vitae* (CV) that was attached as Exhibit 1 to my May 2002 Declaration. My CV remains essentially unchanged from my May 2002 Declaration.<sup>1</sup>

2. As its scientific consultant, I have again been asked by Enzo Biochem, Inc., on behalf of its wholly-owned subsidiary, Enzo Life Sciences, Inc., to review the latest prosecution development in this application since the submission of Applicants' May 28, 2002 Reply Under 37 C.F.R. §1.111 (In Response To The November 26, 2002 Office Action) and their June 27, 2002 Supplemental Response (To Applicants' May 28, 2002 Reply Under 37 C.F.R. §1.111).<sup>2</sup> This latest development takes the form of an office action mailed on October 8, 2002. I have read and reviewed the October 8, 2002 Office Action and claims 736-825 that are cited on page 5, item no. 8, in that document. As part of my review that culminated in the submission of my May 2002 Declaration, I had reviewed claims 736-825, together with other claims (576-735)<sup>3</sup>. In general, the subject matter of claims 736-825 is now directed to an oligo- or polynucleotide comprising at least one modified nucleotide in which a non-radioactive moiety label Sig is directly detected when covalently attached to the phosphate moiety of at least one modified nucleotide in the oligo- or polynucleotide. The covalent attachment of the Sig to the phosphate moiety is through a chemical linkage comprising a

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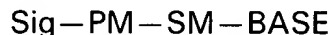
<sup>1</sup> Since my May 2002 Declaration, I have written a review chapter on immunology that will be published in the next edition of Topley & Wilson's microbiology textbook. The textbook which includes my chapter is slated to be published next year (2003).

<sup>2</sup> Applicants' June 27, 2002 Supplemental Response also included the submission of the Declaration of Dr. Alexander A. Waldrop, III. Soon after its filing, I was given a copy of Applicants' June 27, 2002 Supplemental Response, including Dr. Waldrop's Declaration.

<sup>3</sup> A complete set of pending claims 576-825 was attached as Exhibit 6 to my May 2002 Declaration.

polypeptide. Claim 736 is directed to such subject matter and is reproduced below.<sup>4</sup>

736. (Amended) An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the formula



wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a base moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM through a chemical linkage comprising a polypeptide, and said Sig comprising a non-radioactive label moiety which can be directly detected when indirectly attached to PM through said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

A description of claims 736-825 was also given in my May 2002 Declaration (Section 9, page 7; Section 9 A (ii), page 8; Section 9 B (ii), page 10; Section 9 C (ii), pages 10-11; Section 9 D (ii), page 12; and Section 9 E, page 12).

3. I have read in the October 8, 2002 Office Action that claims 736-825 were rejected for new matter. In the Office Action (Item No. 8, page 5), the Examiner stated that these claims contain:

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<sup>4</sup> I have been informed by Enzo Biochem's attorney that changes will be made to the claims as follows:

claims 581, 583, 601, 603, 622, 624, 642, 644, 663, 665, 682, 684, 702, 704, 721, 723, 736, 740, 741, 748, 751, 755, 759, 760, 767, 770, 775, 779, 780, 787, 790, 794, 798, 799, 806, 809, 814, 816, 817, 819, 820, 822, 823 and 825 will be amended;

claims 577, 597, 618, 638, 659, 678, 698, 717, 737, 756, 776 and 795 will be canceled. Thus, upon entry of these claim changes and cancellations, the pending claims will include 576, 578-596, 598-617, 619-637, 639-658, 660-677, 679-697, 699-716, 718-736, 738-755, 757-775, 777-794 and 796-825. A copy of the last-mentioned pending claims is attached to my Supplemental Declaration as Exhibit 1.

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

These claims recite, "Sig being covalently attached to PM through a chemical linkage comprising a polypeptide or a protein", which is not supported in the specification, and therefore, constitutes new matter.

If Applicants' traverse this rejection, Applicants' should specifically identify (by page and line number), where the specification provides support for these claims.

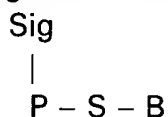
4. As Enzo's scientific consultant, I am making this Supplemental Declaration to present evidence that the subject matter of claims 736-825 (included as Exhibit 1 herewith) in which a non-radioactive label moiety Sig is covalently attached to the phosphate moiety via a polypeptide chemical linkage is supported by the originally filed Engelhardt specification. As in the case of my May 2002 Declaration, I am also being compensated by Enzo for making this Supplemental Declaration on its behalf. As described in my May 2002 Declaration (Section 12, page 13), I consider myself to possess the requisite level of skill and knowledge of a person skilled in the art to which the present application and invention pertains.

5. As a person skilled in the art, it is my opinion and conclusion that as originally filed in June 1982, the Engelhardt specification supports the subject matter of claims 736-825 to be presented in Applicants' October 28, 2002 Amendment Under 37 C.F.R. §1.116. To state it in another way, it is my opinion and conclusion as a skilled artisan that the Engelhardt specification reasonably conveys that Applicants were in possession of the subject matter of claims 736-825 with respect to the chemical linkage comprising a polypeptide when the

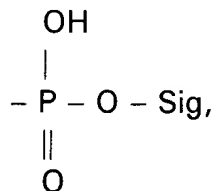
Engelhardt application was first filed in June 1982. My reasons are set forth in the next several paragraphs below.<sup>5</sup>

6. I note that the claims originally filed with the Engelhardt specification included claims 141, 143 and 167 as follows:

141. A nucleotide having the general formula



wherein P is the phosphoric acid moiety, S the sugar moiety and B the base moiety, the phosphoric acid moiety being attached to the 3' and/or the 5' position of the sugar moiety when said nucleotide is a deoxyribonucleotide and at the 2', 3' and/or 5' position when said nucleotide is a ribonucleotide, said base B being a purine or pyrimidine, said base B being attached from the N1 position or the N9 position to the 1' position of the sugar moiety when said base B is a pyrimidine or a purine, respectively, and wherein Sig is a chemical moiety covalently attached to the phosphoric acid moiety via the chemical linkage

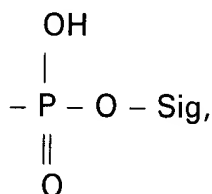


said Sig, when attached to said phosphoric acid moiety P being capable of signalling itself or making itself self-detecting or its presence known.

143. A nucleotide having the general formula P-S-B, wherein P is the phosphoric acid moiety, S the sugar or monosaccharide moiety and B the base moiety, said nucleotide having covalently attached to the P or S or B moiety a chemical moiety Sig, said Sig chemical moiety when attached to the P moiety is attached thereto via the chemical linkage,

<sup>5</sup> Any opinions and conclusions in this Supplemental Declaration continue to be given in light of my training, background and experience as a person of at least ordinary skill in the art.





said when Sig is attached to the S moiety, the S moiety is a ribose group, said chemical moiety Sig when attached to said P, S or B being capable of signalling itself or makes itself self-detecting or its presence known.

167. A polynucleotide comprising one or more nucleotides in accordance with Claim 1 or Claim 101 or Claim 141 or Claim 142 or Claim 143, coupled or attached to a polypeptide, said polypeptide having attached thereto one or more Sig chemical moieties, said Sig when attached to said polypeptide being capable of signalling itself or making itself self-detecting or its presence known.

7. As a person skilled in the art to which the Engelhardt invention pertains, it is my opinion and conclusion that originally filed claims 141, 143 and 167 reasonably convey that Applicants had possession of the subject matter of claims 736-825 at the time the Engelhardt application was first filed in June 1982. More particularly, originally filed claim 167 recites:

[a] ***polynucleotide comprising one or more nucleotides*** in accordance with . . . Claim 141 or . . . Claim 143, ***coupled or attached to a polypeptide, said polypeptide having attached thereto one or more Sig chemical moieties***, said Sig when attached to said polypeptide being capable of signalling itself or making itself self-detecting or its presence known. [emphasis added]

Both originally filed claims 141 and 143 recite subject matter in which

Sig is a chemical moiety covalently to the phosphoric acid moiety [phosphate moiety]" (claim 141),

and

said nucleotide having covalently attached to the P . . . moiety a chemical moiety Sig, (claim 143).

Taken together, these three claims provide a description that reasonably conveys to me that non-radioactive label moieties Sig are covalently attached to the phosphate moieties through chemical linkages comprising polypeptides, as set forth in claims 736-825 (Exhibit 1).

8. It is also disclosed in the Engelhardt specification (Example V, page 57):

Biotin and polybiotinylated poly-L-lysine were coupled to oligoribonucleotides using a carbodiimide coupling procedure described by Halloran and Parker, J. Immunology., 96 373 (1966). As an example, DNA (1 µg/ml, 1 ml) in tris buffer pH 8.2, sheared with 0.1 N sodium hydroxide was denatured by boiling for 10 minutes and quick cooling in an ice bath. Biotinyl-1,6-diaminohexane amide (2 mg, 6 µmol) or polybiotinylated poly-L-lysine (2 mg) and 1-ethyl-3-diisopropylaminocarbodiimide HCl (10 mg, 64 µmol) were added, and the pH readjusted to 8.2. After 24 hours at room temperature in the dark, the mixture was dialyzed against 10 mM tris buffered saline. DNA was precipitated ethanol.

As a person skilled in the art, it is my opinion and conclusion that Example V in the Engelhardt specification discloses an oligoribonucleotide in which non-radioactive label moieties Sig, i.e., biotin molecules, are covalently attached to a phosphate moiety of the oligoribonucleotide through a chemical linkage comprising a polypeptide, i.e., poly-L-lysine.

9. In summary, it is my opinion and conclusion as a person skilled in the art to which claims 736-825 pertain, that the Engelhardt specification (specifically, Example V, page 57) and the originally filed claims (141, 143 and 167) reasonably conveys that Applicants had possession of their claimed subject matter wherein non-radioactive label moieties Sig are covalently attached to phosphate moieties

through chemical linkages comprising polypeptides.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

10/26/02  
Date

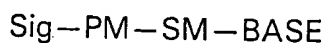
Charles W. Parker MD  
Charles W. Parker, M.D.

\* \* \* \* \*

*FinalSupplDecl.CWP.10.25.02*

EXHIBIT 1 TO DECLARATION OF DR. CHARLES W. PARKER

576. An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the formula

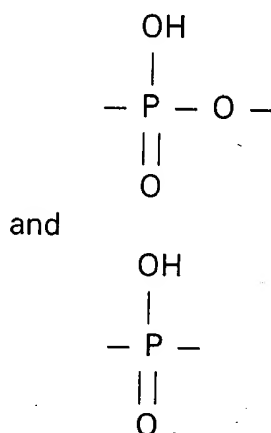


wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a base moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM directly or through a chemical linkage, said Sig comprising a non-polypeptide, non-radioactive label moiety which can be directly or indirectly detected when attached to PM or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

~~577. (Canceled) The oligo- or polydeoxyribonucleotide of claim 576, wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

578. The oligo- or polydeoxyribonucleotide of claim 576, wherein said Sig moiety comprises at least three carbon atoms.

579. The oligo- or polydeoxyribonucleotide of claim 576, wherein said covalent attachment is selected from the group consisting of

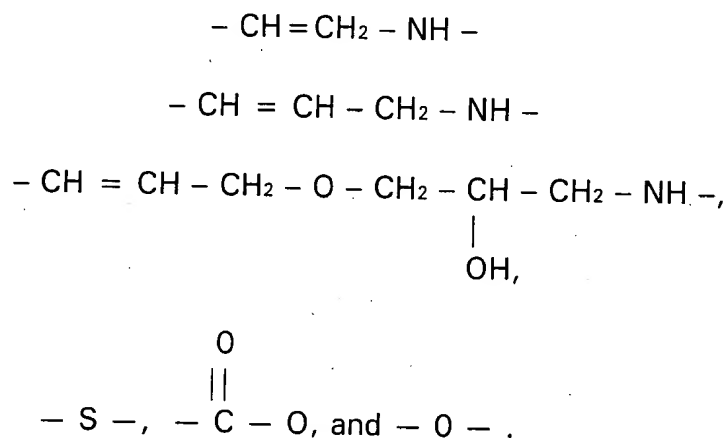


580. The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

581. (Amended) The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage comprises a -CH<sub>2</sub>NH- moiety.

582. The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage comprises an allylamine group.

583. (Amended) The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage comprises any of the moieties:



584. The oligo- or polydeoxyribonucleotide of claim 576, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

585. The oligo- or polydeoxyribonucleotide of claim 576, wherein said PM is monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached to said PM through a phosphorus atom or phosphate oxygen.

586. The oligo- or polydeoxyribonucleotide of claim 576, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

587. The oligo- or polydeoxyribonucleotide of claim 586, wherein said electron dense component comprises ferritin.

588. The oligo- or polydeoxyribonucleotide of claim 586, wherein said magnetic component comprises magnetic oxide.

589. The oligo- or polydeoxyribonucleotide of claim 588, wherein said magnetic oxide comprises ferric oxide.

590. The oligo- or polydeoxyribonucleotide of claim 586, wherein said metal-containing component is catalytic.

591. The oligo- or polydeoxyribonucleotide of claim 586, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

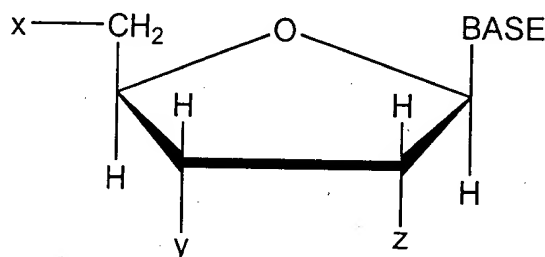
592. The oligo- or polydeoxyribonucleotide of claim 576, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

593. The oligo- or polydeoxyribonucleotide of claim 592, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.

594. The oligo- or polydeoxyribonucleotide of claim 592, wherein the sugar moiety of said terminal nucleotide has oxygen atoms at each of the 2' and 3' positions thereof.

595. The oligo- or polydeoxyribonucleotide of claim 576, comprising at least one ribonucleotide.

596. An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

wherein Sig is covalently attached directly or through a chemical linkage to at least one phosphate selected from the group consisting of x, y, z, and a combination thereof, said Sig comprising a non-polypeptide, non-radioactive label moiety which

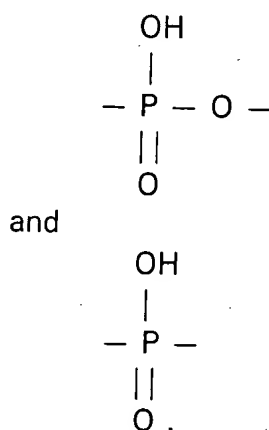


can be directly or indirectly detected when so attached to said phosphate or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

~~597. (Canceled) The oligo- or polydeoxyribonucleotide of claim 596, wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

598. The oligo- or polydeoxyribonucleotide of claim 596, wherein said Sig moiety comprises at least three carbon atoms.

599. The oligo- or polydeoxyribonucleotide of claim 596, wherein said covalent attachment is selected from the group consisting of

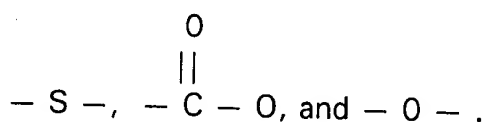
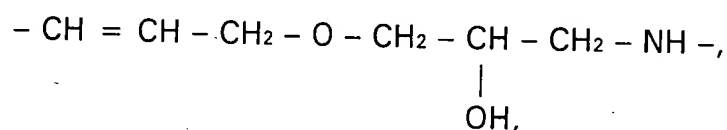
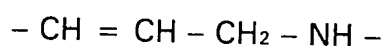
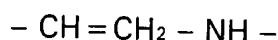


600. The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

601. (Amended) The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage comprises a  $-\text{CH}_2\text{NH}-$  moiety.

602. The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage comprises an allylamine group.

603. (Amended) The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage comprises any of the moieties:



604. The oligo- or polydeoxyribonucleotide of claim 596, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

605. The oligo- or polydeoxyribonucleotide of claim 596, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and said Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or phosphate oxygen.

606. The oligo- or polydeoxyribonucleotide of claim 596, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

607. The oligo- or polydeoxyribonucleotide of claim 606, wherein said electron dense component comprises ferritin.

608. The oligo- or polydeoxyribonucleotide of claim 606, wherein said magnetic component comprises magnetic oxide.

609. The oligo- or polydeoxyribonucleotide of claim 608, wherein said magnetic oxide comprises ferric oxide.

610. The oligo- or polydeoxyribonucleotide of claim 606, wherein said metal-containing component is catalytic.

611. The oligo- or polydeoxyribonucleotide of claim 606, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

612. The oligo- or polydeoxyribonucleotide of claim 596, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

613. The oligo- or polydeoxyribonucleotide of claim 612, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.

614. The oligo- or polydeoxyribonucleotide of claim 612, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.

615. The oligo- or polydeoxyribonucleotide of claim 596, comprising at least one ribonucleotide.

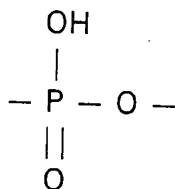


and Sig being covalently attached to PM directly or via a chemical linkage, said Sig comprising a non-polypeptide, non-radioactive label moiety which can be directly or indirectly detected when attached to PM or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide, and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

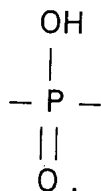
~~618. (Canceled) The oligo- or polynucleotide of claim 617, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

619. The oligo- or polynucleotide of claim 617, wherein said Sig moiety comprises at least three carbon atoms.

620. The oligo- or polynucleotide of claim 617, wherein said covalent attachment is selected from the group consisting of



and

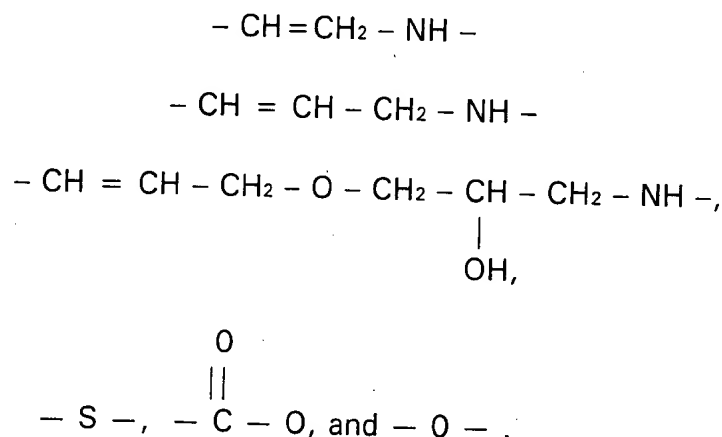


621. The oligo- or polynucleotide of claim 617, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

622. (Amended) The oligo- or polynucleotide of claim 617, wherein said chemical linkage comprises a  $-\text{CH}_2\text{NH}-$  moiety.

623. The oligo- or polynucleotide of claim 617, wherein said chemical linkage comprises an allylamine group.

624. (Amended) The oligo- or polynucleotide of claim 617, wherein said chemical linkage comprises any of the moieties:



625. The oligo- or polynucleotide of claim 617, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

626. The oligo- or polynucleotide of claim 617, wherein said PM is a monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached to said PM through a phosphorus atom or a phosphate oxygen.

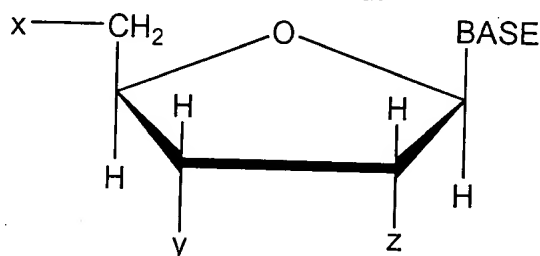
627. The oligo- or polynucleotide of claim 617, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.



628. The oligo- or polynucleotide of claim 627, wherein said electron dense component comprises ferritin.
629. The oligo- or polynucleotide of claim 627, wherein said magnetic component comprises magnetic oxide.
630. The oligo- or polynucleotide of claim 629, wherein said magnetic oxide comprises ferric oxide.
631. The oligo- or polynucleotide of claim 627, wherein said metal-containing component is catalytic.
632. The oligo- or polynucleotide of claim 627, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.
633. The oligo- or polynucleotide of claim 617, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polynucleotide.
634. The oligo- or polynucleotide of claim 633, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.
635. The oligo- or polynucleotide of claim 633, wherein the sugar moiety of said terminal nucleotide has an oxygen atom at each of the 2' and 3' positions thereof.

636. The oligo- or polynucleotide of claim 617, comprising at least one deoxyribonucleotide.

637. An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

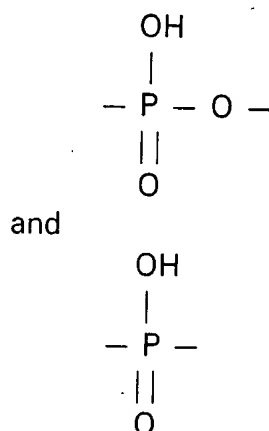
wherein Sig is covalently attached directly or through a chemical linkage to at least one phosphate selected from the group consisting of x, y and z, and a combination thereof, said Sig comprising a non-polypeptide, non-radioactive label moiety which can be directly or indirectly detected when so attached to said phosphate or when said modified nucleotide is incorporated into said oligo- or

polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

~~638. (Canceled) The oligo- or polynucleotide of claim 637, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

639. The oligo- or polynucleotide of claim 637, wherein said Sig moiety comprises at least three carbon atoms.

640. The oligo- or polynucleotide of claim 637, wherein said covalent attachment is selected from the group consisting of

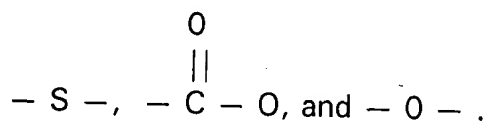
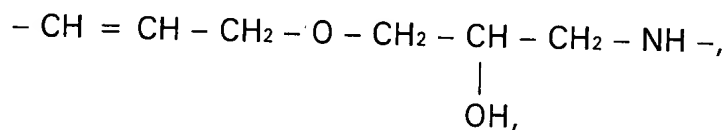
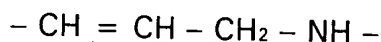


641. The oligo- or polynucleotide of claim 637, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

642. (Amended) The oligo- or polynucleotide of claim 637, wherein said chemical linkage comprises -CH<sub>2</sub>NH- moiety.

643. The oligo- or polynucleotide of claim 637, wherein said chemical linkage comprises an allylamine group.

644. (Amended) The oligo- or polynucleotide of claim 637, wherein said chemical linkage comprises any of the moieties:



645. The oligo- or polynucleotide of claim 637, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

646. The oligo- or polynucleotide of claim 637, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or a phosphate oxygen.

647. The oligo- or polynucleotide of claim 637, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

648. The oligo- or polynucleotide of claim 647, wherein said electron dense component comprises ferritin.

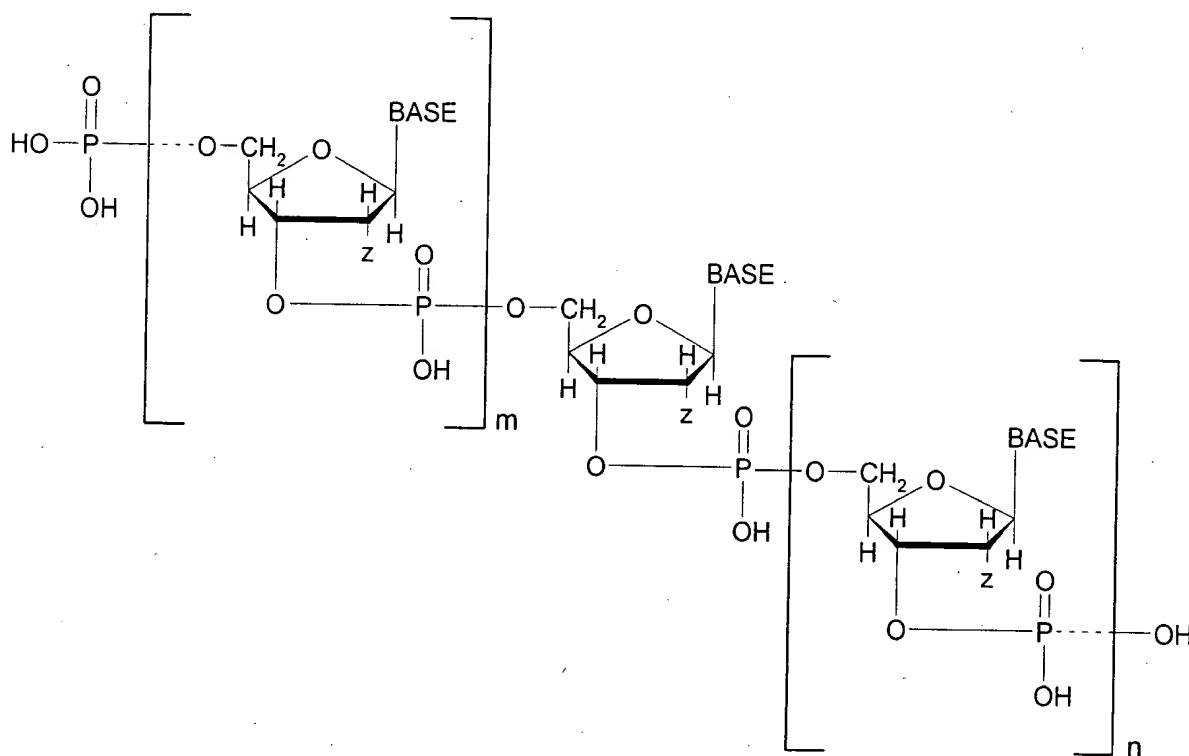
649. The oligo- or polynucleotide of claim 647, wherein said magnetic component comprises magnetic oxide.

650. The oligo- or polynucleotide of claim 649, wherein said magnetic oxide comprises ferric oxide.

651. The oligo- or polynucleotide of claim 647, wherein said metal-containing component is catalytic.

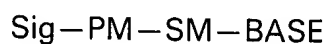
652. The oligo- or polynucleotide of claim 647, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.
653. The oligo- or polynucleotide of claim 637, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polynucleotide.
654. The oligo- or polynucleotide of claim 653, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.
655. The oligo- or polynucleotide of claim 653, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.
656. The oligo- or polynucleotide of claim 637, comprising at least one deoxyribonucleotide.

657. The oligo- or polynucleotide of claim 637, having the structural formula:



wherein m and n represent integers from 0 up to about 100,000, and wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula.

658. An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the formula



wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a base moiety selected from the group consisting of a pyrimidine, a purine and a

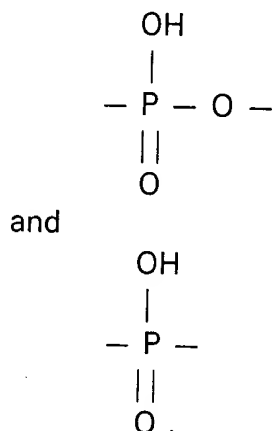
deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM directly or through a chemical linkage, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to PM or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, and wherein Sig comprises biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

~~659. (Canceled) The oligo- or polydeoxyribonucleotide of claim 658, wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

660. The oligo- or polydeoxyribonucleotide of claim 658, wherein said Sig moiety comprises at least three carbon atoms.



661. The oligo- or polydeoxyribonucleotide of claim 658, wherein said covalent attachment is selected from the group consisting of

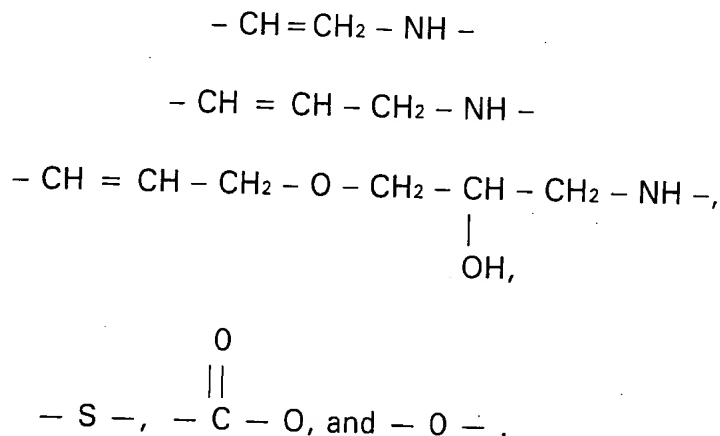


662. The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

663. (Amended) The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage comprises a -CH<sub>2</sub>NH- moiety.

664. The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage comprises an allylamine group.

665. (Amended) The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage comprises any of the moieties:



666. The oligo- or polydeoxyribonucleotide of claim 658, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

667. The oligo- or polydeoxyribonucleotide of claim 658, wherein said PM is monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached to said PM through a phosphorus atom or phosphate oxygen.

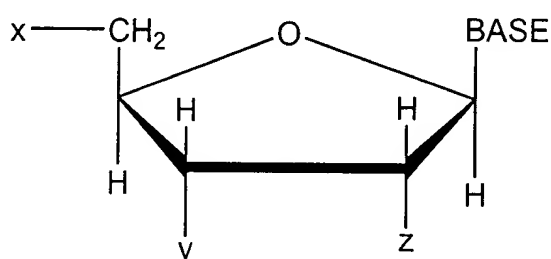
668. The oligo- or polydeoxyribonucleotide of claim 658, wherein said electron dense component comprises ferritin.

669. The oligo- or polydeoxyribonucleotide of claim 658, wherein said magnetic component comprises magnetic oxide.

670. The oligo- or polydeoxyribonucleotide of claim 658, wherein said magnetic oxide comprises ferric oxide.

671. The oligo- or polydeoxyribonucleotide of claim 658, wherein said metal-containing component is catalytic.
672. The oligo- or polydeoxyribonucleotide of claim 658, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.
673. The oligo- or polydeoxyribonucleotide of claim 658, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.
674. The oligo- or polydeoxyribonucleotide of claim 673, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.
675. The oligo- or polydeoxyribonucleotide of claim 673, wherein the sugar moiety of said terminal nucleotide has oxygen atoms at each of the 2' and 3' positions thereof.
676. The oligo- or polydeoxyribonucleotide of claim 658, comprising at least one ribonucleotide.

677. An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

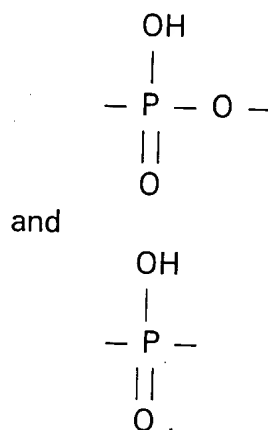
wherein Sig is covalently attached directly or through a chemical linkage to at least one phosphate selected from the group consisting of x, y, z, and a combination thereof, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when so attached to said phosphate or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, wherein Sig comprises biotin,

iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

~~678. (Canceled) The oligo- or polydeoxyribonucleotide of claim 677, wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

679. The oligo- or polydeoxyribonucleotide of claim 677, wherein said Sig moiety comprises at least three carbon atoms.

680. The oligo- or polydeoxyribonucleotide of claim 677, wherein said covalent attachment is selected from the group consisting of

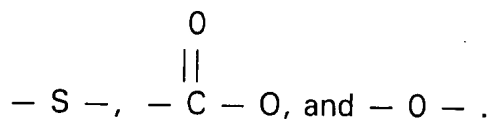
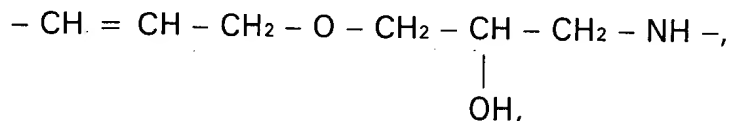


681. The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

682. (Amended) The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage comprises a  $-\text{CH}_2\text{NH}-$  moiety.

683. The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage comprises an allylamine group.

684. (Amended) The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage comprises any of the moieties:



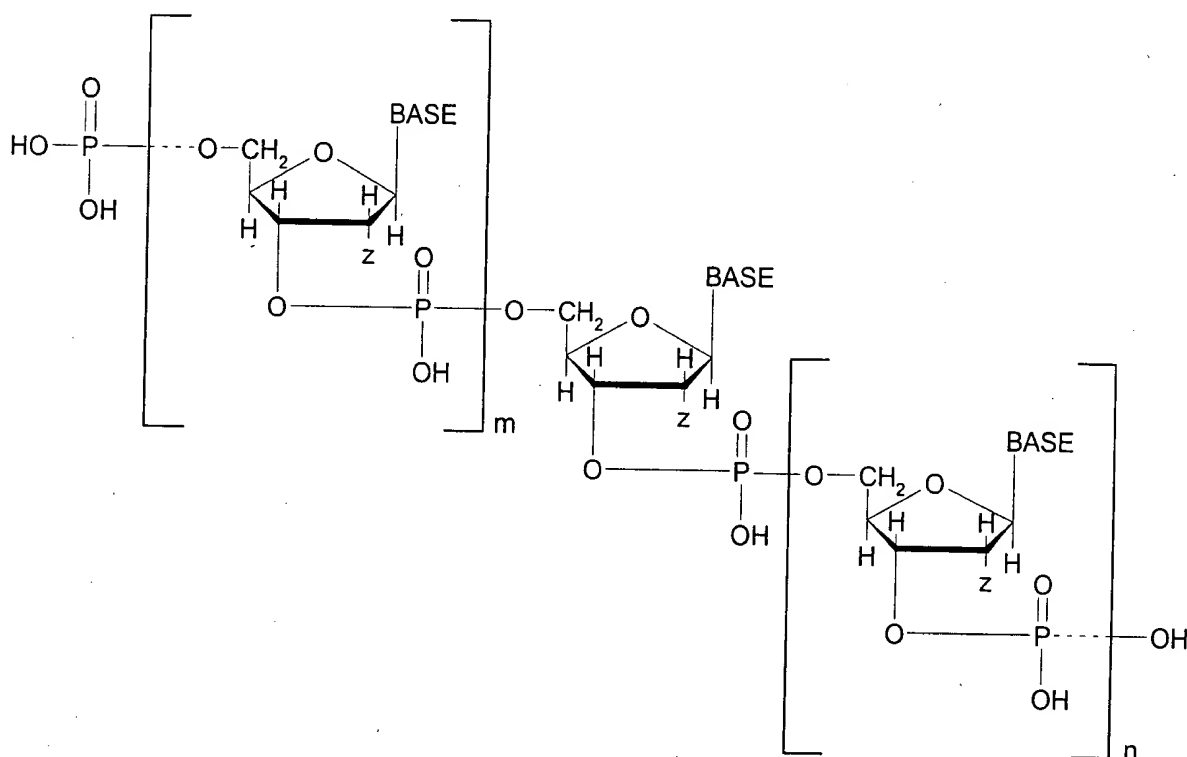
685. The oligo- or polydeoxyribonucleotide of claim 677, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

686. The oligo- or polydeoxyribonucleotide of claim 677, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and said Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or phosphate oxygen.

687. The oligo- or polydeoxyribonucleotide of claim 677, wherein said electron dense component comprises ferritin.
688. The oligo- or polydeoxyribonucleotide of claim 677, wherein said magnetic component comprises magnetic oxide.
689. The oligo- or polydeoxyribonucleotide of claim 688, wherein said magnetic oxide comprises ferric oxide.
690. The oligo- or polydeoxyribonucleotide of claim 677, wherein said metal-containing component is catalytic.
691. The oligo- or polydeoxyribonucleotide of claim 677, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.
692. The oligo- or polydeoxyribonucleotide of claim 677, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.
693. The oligo- or polydeoxyribonucleotide of claim 692, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.
694. The oligo- or polydeoxyribonucleotide of claim 692, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.

695. The oligo- or polydeoxyribonucleotide of claim 677, comprising at least one ribonucleotide.

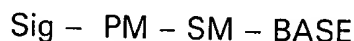
696. The oligo- or polydexoyribonucleotide of claim 677, having the structural formula:



wherein m and n represent integers from 0 up to about 100,000, and wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula.



697. An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the formula

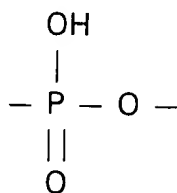


wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM directly or via a chemical linkage, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to PM or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide, and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide, wherein Sig comprises biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

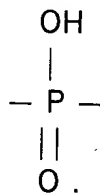
~~698. (Canceled) The oligo- or polynucleotide of claim 697, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

699. The oligo- or polynucleotide of claim 697, wherein said Sig moiety comprises at least three carbon atoms.

700. The oligo- or polynucleotide of claim 697, wherein said covalent attachment is selected from the group consisting of



and

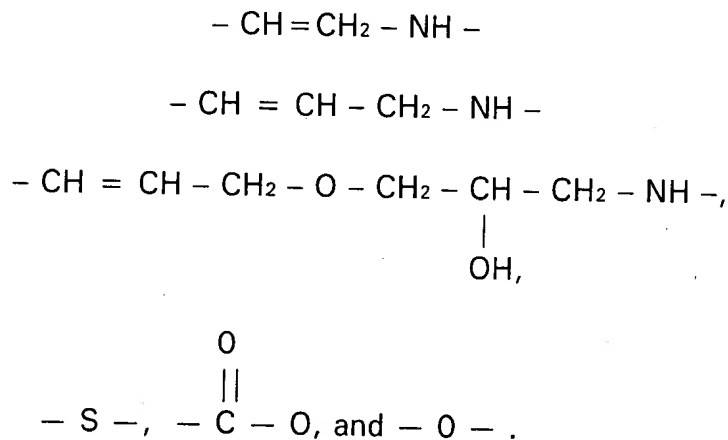


701. The oligo- or polynucleotide of claim 697, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

702. (Amended) The oligo- or polynucleotide of claim 697, wherein said chemical linkage comprises a  $-\text{CH}_2\text{NH}-$  moiety.

703. The oligo- or polynucleotide of claim 697, wherein said chemical linkage comprises an allylamine group.

704. (Amended) The oligo- or polynucleotide of claim 697, wherein said chemical linkage comprises any of the moieties:



705. The oligo- or polynucleotide of claim 697, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

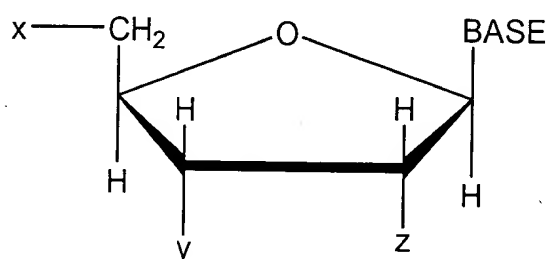
706. The oligo- or polynucleotide of claim 697, wherein said PM is a monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached to said PM through a phosphorus atom or a phosphate oxygen.

707. The oligo- or polynucleotide of claim 697, wherein said electron dense component comprises ferritin.

708. The oligo- or polynucleotide of claim 697, wherein said magnetic component comprises magnetic oxide.

709. The oligo- or polynucleotide of claim 708, wherein said magnetic oxide comprises ferric oxide.
710. The oligo- or polynucleotide of claim 697, wherein said metal-containing component is catalytic.
711. The oligo- or polynucleotide of claim 697, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.
712. The oligo- or polynucleotide of claim 697, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polynucleotide.
713. The oligo- or polynucleotide of claim 712, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.
714. The oligo- or polynucleotide of claim 712, wherein the sugar moiety of said terminal nucleotide has an oxygen atom at each of the 2' and 3' positions thereof.
715. The oligo- or polynucleotide of claim 697, comprising at least one deoxyribonucleotide.

716. An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

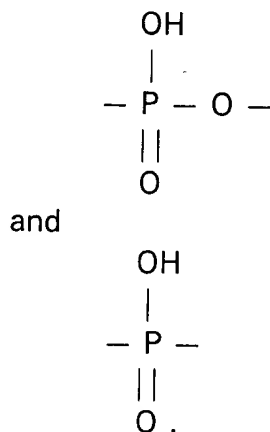
wherein Sig is covalently attached directly or through a chemical linkage to at least one phosphate selected from the group consisting of x, y and z, and a combination thereof, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when so attached to said phosphate or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an

oligoribonucleotide or a polyribonucleotide and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide, wherein Sig comprises biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

~~717. (Canceled) The oligo- or polynucleotide of claim 716, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

718. The oligo- or polynucleotide of claim 716, wherein said Sig moiety comprises at least three carbon atoms.

719. The oligo- or polynucleotide of claim 716, wherein said covalent attachment is selected from the group consisting of

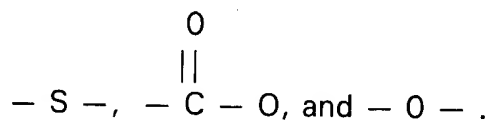
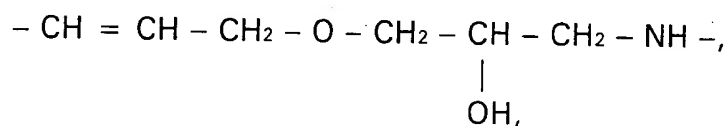
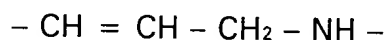


720. The oligo- or polynucleotide of claim 716, wherein said chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

721. (Amended) The oligo- or polynucleotide of claim 716, wherein said chemical linkage comprises a  $-\text{CH}_2\text{NH}-$  moiety.

722. The oligo- or polynucleotide of claim 716, wherein said chemical linkage comprises an allylamine group.

723. (Amended) The oligo- or polynucleotide of claim 716, wherein said chemical linkage comprises any of the moieties:



724. The oligo- or polynucleotide of claim 716, wherein said chemical linkage of Sig includes a glycosidic linkage moiety.

725. The oligo- or polynucleotide of claim 716, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or a phosphate oxygen.

726. The oligo- or polynucleotide of claim 716, wherein said electron dense component comprises ferritin.

727. The oligo- or polynucleotide of claim 716, wherein said magnetic component comprises magnetic oxide.

728. The oligo- or polynucleotide of claim 727, wherein said magnetic oxide comprises ferric oxide.

729. The oligo- or polynucleotide of claim 716, wherein said metal-containing component is catalytic.

730. The oligo- or polynucleotide of claim 716, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

731. The oligo- or polynucleotide of claim 716, wherein said Sig moiety is attached to a terminal nucleotide in said oligo- or polynucleotide.

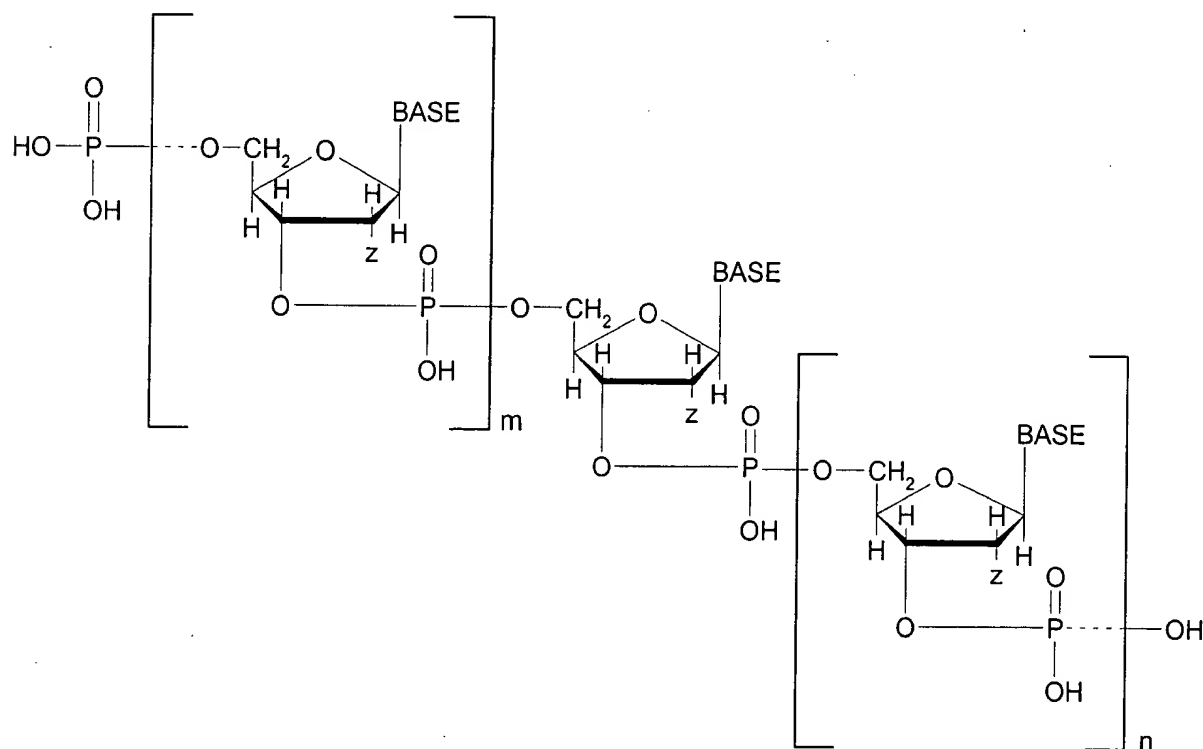


732. The oligo- or polynucleotide of claim 731, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.

733. The oligo- or polynucleotide of claim 731, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.

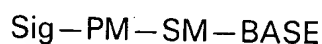
734. The oligo- or polynucleotide of claim 716, comprising at least one deoxyribonucleotide.

735. The oligo- or polynucleotide of claim 716, having the structural formula:



wherein m and n represent integers from 0 up to about 100,000, and wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula.

736. (Amended) An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the formula

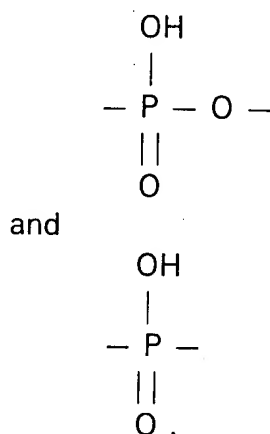


wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a base moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM through a chemical linkage comprising a polypeptide, and said Sig comprising a non-radioactive label moiety which can be directly detected when indirectly attached to PM through said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polydeoxyribonucleotide or when said oligo- or polydeoxyribonucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof.

~~737. (Canceled) The oligo- or polydeoxyribonucleotide of claim 736, wherein said Sig is or renders the nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

738. The oligo- or polydeoxyribonucleotide of claim 736, wherein said Sig moiety comprises at least three carbon atoms.

739. The oligo- or polydeoxyribonucleotide of claim 736, wherein said covalent attachment is selected from the group consisting of



740. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

741. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said PM is monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached via said polypeptide chemical linkage to said PM through a phosphorus atom or phosphate oxygen.

742. The oligo- or polydeoxyribonucleotide of claim 736, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

743. The oligo- or polydeoxyribonucleotide of claim 742, wherein said electron dense component comprises ferritin.

744. The oligo- or polydeoxyribonucleotide of claim 742, wherein said magnetic component comprises magnetic oxide.

745. The oligo- or polydeoxyribonucleotide of claim 744, wherein said magnetic oxide comprises ferric oxide.

746. The oligo- or polydeoxyribonucleotide of claim 742, wherein said metal-containing component is catalytic.

747. The oligo- or polydeoxyribonucleotide of claim 742, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

748. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said oligo- or polydeoxyribonucleotide is terminally ligated or attached to said polypeptide chemical linkage.

749. The oligo- or polydeoxyribonucleotide of claim 736, wherein said polypeptide comprises polylysine.

750. The oligo- or polydeoxyribonucleotide of claim 736, wherein said polypeptide is selected from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

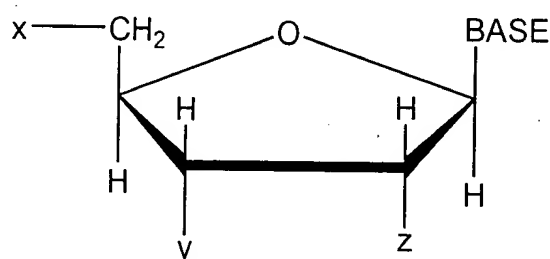
751. (Amended) The oligo- or polydeoxyribonucleotide of claim 736, wherein said Sig moiety is attached via said polypeptide chemical linkage to a phosphate moiety in a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

752. The oligo- or polydeoxyribonucleotide of claim 751, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.

753. The oligo- or polydeoxyribonucleotide of claim 751, wherein the sugar moiety of said terminal nucleotide has oxygen atoms at each of the 2' and 3' positions thereof.

754. The oligo- or polydeoxyribonucleotide of claim 736, comprising at least one ribonucleotide.

755. (Amended) An oligo- or polydeoxyribonucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polydeoxyribonucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

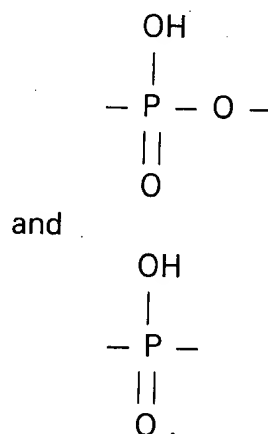
wherein Sig is covalently attached through a chemical linkage to at least one phosphate selected from the group consisting of x, y, z, and a combination thereof, said chemical linkage comprising a polypeptide, and said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to said phosphate via said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polydeoxynucleotide or when said oligo- or polydeoxynucleotide is hybridized to said complementary nucleic acid of

interest or a portion thereof.

~~756. (Canceled) The oligo- or polydeoxyribonucleotide of claim 755, wherein said Sig is or renders the modified nucleotide or the oligo- or polydeoxyribonucleotide self-signaling or self-indicating or self-detecting.~~

757. The oligo- or polydeoxyribonucleotide of claim 755, wherein said Sig moiety comprises at least three carbon atoms.

758. The oligo- or polydeoxyribonucleotide of claim 755, wherein said covalent attachment is selected from the group consisting of



759. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

760. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and said Sig moiety is covalently attached via said polypeptide chemical linkage to either or both of said x and y through a phosphorus atom or phosphate oxygen.

761. The oligo- or polydeoxyribonucleotide of claim 755, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component, or a combination of any of the foregoing.

762. The oligo- or polydeoxyribonucleotide of claim 761, wherein said electron dense component comprises ferritin.

763. The oligo- or polydeoxyribonucleotide of claim 761, wherein said magnetic component comprises magnetic oxide.

764. The oligo- or polydeoxyribonucleotide of claim 763, wherein said magnetic oxide comprises ferric oxide.

765. The oligo- or polydeoxyribonucleotide of claim 761, wherein said metal-containing component is catalytic.



766. The oligo- or polydeoxyribonucleotide of claim 761, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

767. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said oligo- or polydeoxyribonucleotide is terminally ligated or attached to said polypeptide chemical linkage.

768. The composition of claim 755, wherein said polypeptide comprises polylysine.

769. The composition of claim 755, wherein said polypeptide is selected from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

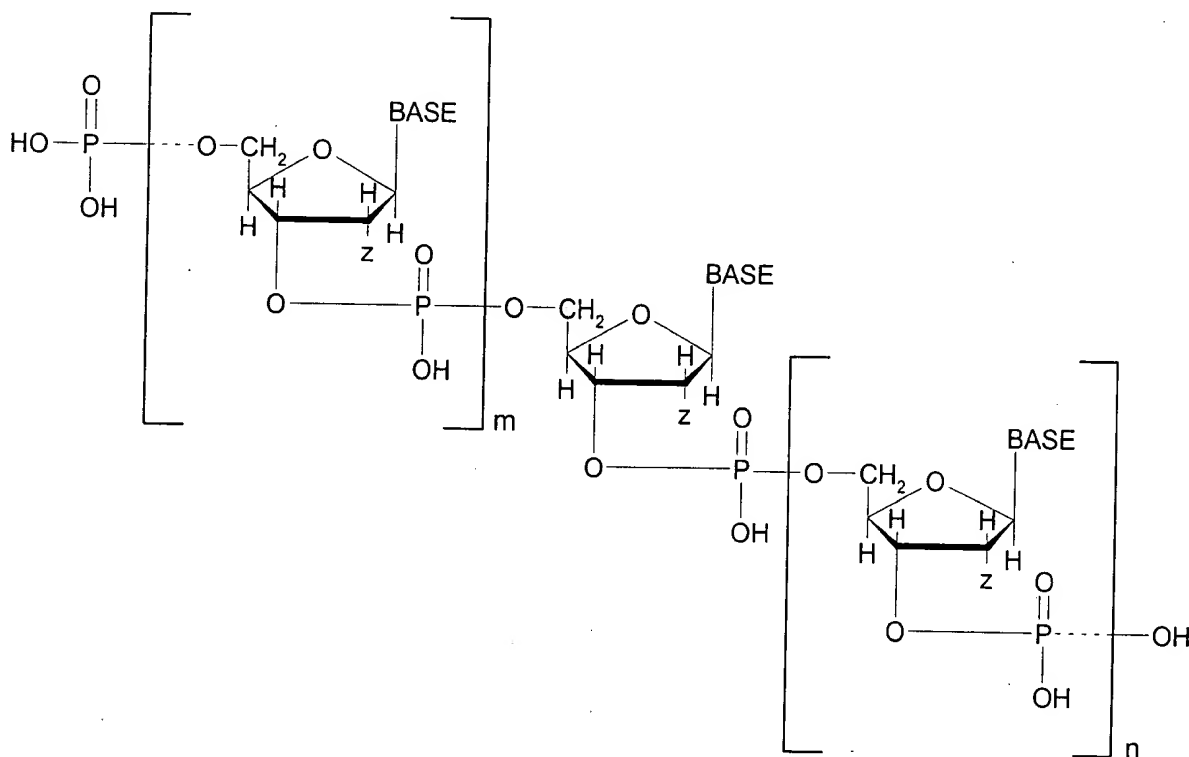
770. (Amended) The oligo- or polydeoxyribonucleotide of claim 755, wherein said Sig moiety is attached via said polypeptide chemical linkage to a terminal nucleotide in said oligo- or polydeoxyribonucleotide.

771. The oligo- or polydeoxyribonucleotide of claim 770, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.

772. The oligo- or polydeoxyribonucleotide of claim 770, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.

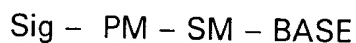
773. The oligo- or polydeoxyribonucleotide of claim 755, comprising at least one ribonucleotide.

774. The oligo- or polydeoxyribonucleotide of claim 755, having the structural formula:



wherein m and n represent integers from 0 up to about 100,000, and wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula.

775. (Amended) An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the formula

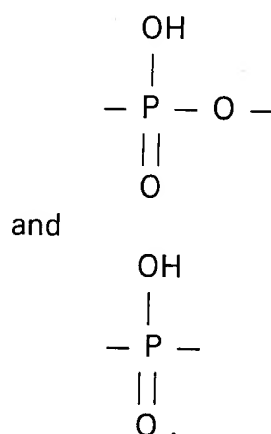


wherein PM is a phosphate moiety, SM is a sugar moiety and BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, said PM being attached to SM, said BASE being attached to SM, and Sig being covalently attached to PM via a chemical linkage comprising a polypeptide, said Sig comprising a non-radioactive label moiety which can be directly or indirectly detected when attached to PM via said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a polyribonucleotide, and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

~~776. (Canceled) The oligo- or polynucleotide of claim 775, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

777. The oligo- or polynucleotide of claim 775, wherein said Sig moiety comprises at least three carbon atoms.

778. The oligo- or polynucleotide of claim 775, wherein said covalent attachment is selected from the group consisting of



779. (Amended) The oligo- or polynucleotide of claim 775, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.

780. (Amended) The oligo- or polynucleotide of claim 775, wherein said PM is a monophosphate, a diphosphate or a triphosphate and said Sig moiety is covalently attached via said polypeptide chemical linkage to said PM through a phosphorus atom or a phosphate oxygen.

781. The oligo- or polynucleotide of claim 775, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

782. The oligo- or polynucleotide of claim 781, wherein said electron dense component comprises ferritin.

783. The oligo- or polynucleotide of claim 781, wherein said magnetic component comprises magnetic oxide.

784. The oligo- or polynucleotide of claim 783, wherein said magnetic oxide comprises ferric oxide.

785. The oligo- or polynucleotide of claim 781, wherein said metal-containing component is catalytic.

786. The oligo- or polynucleotide of claim 781, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

787. (Amended) The oligo- or polynucleotide of claim 775, wherein said oligo- or polynucleotide is terminally ligated or attached to said polypeptide chemical linkage.

788. The oligo- or polynucleotide of claim 775, wherein said polypeptide comprises polylysine.

789. The oligo- or polynucleotide of claim 775, wherein said polypeptide is selected from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

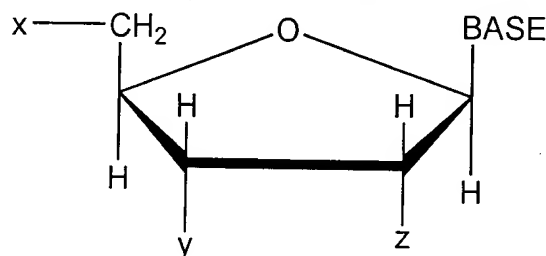
790. (Amended) The oligo- or polynucleotide of claim 775, wherein said Sig moiety is attached via said polypeptide chemical linkage to a terminal nucleotide in said oligo- or polynucleotide.

791. The oligo- or polynucleotide of claim 790, wherein the sugar moiety of said terminal nucleotide has a hydrogen atom at the 2' position thereof.

792. The oligo- or polynucleotide of claim 790, wherein the sugar moiety of said terminal nucleotide has an oxygen atom at each of the 2' and 3' positions thereof.

793. The oligo- or polynucleotide of claim 775, comprising at least one deoxyribonucleotide.

794. (Amended) An oligo- or polynucleotide which is complementary to a nucleic acid of interest or a portion thereof, said oligo- or polynucleotide comprising at least one modified nucleotide having the structural formula:



wherein BASE is a moiety selected from the group consisting of a pyrimidine, a purine and a deazapurine, or analog thereof, and wherein BASE is attached to the 1' position of the pentose ring from the N1 position when BASE is a pyrimidine or from the N9 position when BASE is a purine or a deazapurine;

wherein x is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein y is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate;

wherein z is selected from the group consisting of H—, HO—, a mono-phosphate, a di-phosphate and a tri-phosphate; and

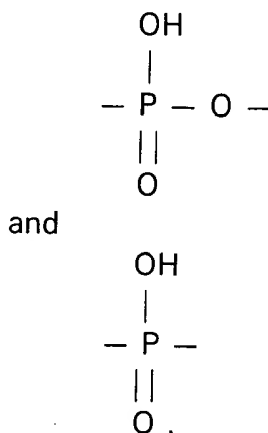
wherein Sig is covalently attached through a chemical linkage to at least one phosphate selected from the group consisting of x, y and z, and a combination thereof, said chemical linkage comprising a polypeptide, and said Sig comprising a non-radioactive label moiety which can be directly detected when attached to said phosphate via said polypeptide chemical linkage or when said modified nucleotide is incorporated into said oligo- or polynucleotide, or when said oligo- or polynucleotide is hybridized to said complementary nucleic acid of interest or a portion thereof, provided that when said oligo- or polynucleotide is an oligoribonucleotide or a

polyribonucleotide and when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

~~795. (Canceled) The oligo- or polynucleotide of claim 794, wherein said Sig is or renders the nucleotide or the oligo- or polynucleotide self-signaling or self-indicating or self-detecting.~~

796. The oligo- or polynucleotide of claim 794, wherein said Sig moiety comprises at least three carbon atoms.

797. The oligo- or polynucleotide of claim 794, wherein said covalent attachment is selected from the group consisting of



798. (Amended) The oligo- or polynucleotide of claim 794, wherein said polypeptide chemical linkage does not interfere substantially with the characteristic ability of Sig to form a detectable signal.



799. (Amended) The oligo- or polynucleotide of claim 794, wherein said x and y each comprise a member selected from the group consisting of a monophosphate, a diphosphate and a triphosphate and Sig moiety is covalently attached to either or both of said x and y through a phosphorus atom or a phosphate oxygen.

800. The oligo- or polynucleotide of claim 794, wherein Sig comprises a component selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, a metal-containing component, a fluorescent component, a chemiluminescent component, a chromogenic component or a combination of any of the foregoing.

801. The oligo- or polynucleotide of claim 800, wherein said electron dense component comprises ferritin.

802. The oligo- or polynucleotide of claim 800, wherein said magnetic component comprises magnetic oxide.

803. The oligo- or polynucleotide of claim 802, wherein said magnetic oxide comprises ferric oxide.

804. The oligo- or polynucleotide of claim 800, wherein said metal-containing component is catalytic.

805. The oligo- or polynucleotide of claim 800, wherein said fluorescent component comprises a member selected from the group consisting of fluorescein, rhodamine and dansyl.

806. (Amended) The oligo- or polynucleotide of claim 794, wherein said oligo- or polynucleotide is terminally ligated or attached to said polypeptide chemical linkage.

807. The oligo- or polynucleotide of claim 794, wherein said polypeptide comprises polylysine.

808. The oligo- or polynucleotide of claim 794, wherein said polypeptide is selected from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

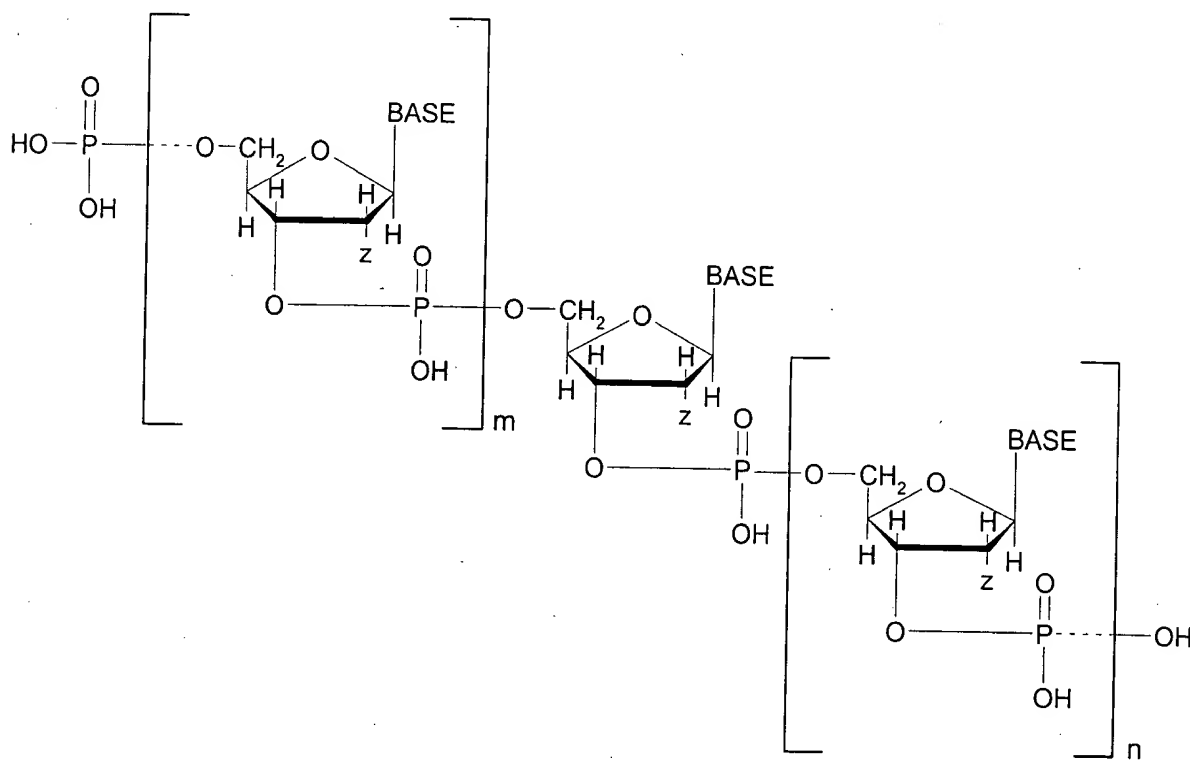
809. (Amended) The oligo- or polynucleotide of claim 794, wherein said Sig moiety is attached via said polypeptide chemical linkage to a terminal nucleotide in said oligo- or polynucleotide.

810. The oligo- or polynucleotide of claim 809, wherein z of said terminal nucleotide comprises a hydrogen atom at the 2' position thereof.

811. The oligo- or polynucleotide of claim 809, wherein both y and z of said terminal nucleotide comprise an oxygen atom at each of the 3' and 2' positions thereof, respectively.

812. The oligo- or polynucleotide of claim 794, comprising at least one deoxyribonucleotide.

813. The oligo- or polynucleotide of claim 794, having the structural formula:



wherein m and n represent integers from 0 up to about 100,000, and wherein said Sig moiety is attached to at least one of the phosphate moieties in said structural formula.

814. (Amended) The oligo- or polydeoxyribonucleotide of claims 576 or 658, wherein said Sig is covalently attached to PM through a chemical linkage comprising a polypeptide.

815. The oligo- or polydeoxyribonucleotide of claim 814, wherein said polypeptide comprises polylysine.

816. (Amended) The oligo- or polydeoxyribonucleotide of claim 814, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

817. (Amended) The oligo- or polydeoxyribonucleotide of claims 596 or 677, wherein said Sig is covalently attached to said at least one phosphate through a chemical linkage comprising a polypeptide.

818. The oligo- or polydeoxyribonucleotide of claim 817, wherein said polypeptide comprises polylysine.

819. (Amended) The oligo- or polydeoxyribonucleotide of claim 817, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

820. (Amended) The oligo- or polynucleotide of claims 617 or 697, wherein said Sig is covalently attached to PM via a chemical linkage comprising a polypeptide.

821. The oligo- or polydeoxyribonucleotide of claim 820, wherein said polypeptide comprises polylysine.

822. (Amended) The oligo- or polydeoxyribonucleotide of claim 820, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

823. (Amended) The oligo- or polynucleotide of claims 637 or 716, wherein said Sig is covalently attached to said at least one phosphate through a chemical linkage comprising a polypeptide.

824. The oligo- or polydeoxyribonucleotide of claim 823, wherein said polypeptide comprises polylysine.

825. (Amended) The oligo- or polydeoxyribonucleotide of claim 824, wherein said polypeptide is selected or derived from the group consisting of avidin, streptavidin and anti-hapten immunoglobulin.

\* \* \* \* \*